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Doctoral Program in Clinical Research

REPRODUCTIVE HEALTH IN FEMALE SURVIVORS OF EARLY ONSET CANCER

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ACADEMIC DISSERTATION

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To my family for their love and support

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ABSTRACT

The development of modern cancer therapies and newer multimodality therapies has led to increased survival in most early onset cancer patients. As more patients experience long-term survival, the late effects of cancer and its treatments affecting both the health and quality of life of survivors have become evident. Female cancer survivors are concerned about the possible adverse effects of cancer and its treatment on their reproductive health. The aim of this study was to evaluate the use of fertility treatments, as well as the risk of adverse pregnancy-related conditions and obstetric outcomes, in female early onset cancer survivors.

In this thesis, Finnish population-based registers were used to compare female cancer survivors to female siblings (Studies I, II and IV) and age-matched female comparison subjects (Study III). The study cohort, which was identified from the Finnish Cancer Registry, comprised female cancer survivors diagnosed with cancer between 1953 and 2004 at the age of 0-34 years (N=13,799) and between 1953 and 2012 at the age of 0-39 years (N=24,610). Female siblings and age-matched comparison subjects were identified by linkage to the Central Population Register. Information on the use of fertility drugs (Study I) was obtained from the Reimbursement Register of Prescribed Medicines. Information on fertility treatments in women giving birth (Study II), as well as information on pregnancy-related conditions (Study III) and obstetric outcomes (Study IV), was retrieved from the Medical Birth Register.

In Study I, we used Poisson regression modelling to estimate incidence rate ratios (IRRs) for the use of fertility drugs, adjusting for attained age and calendar time at fertility drug purchase. In Studies II, III and IV, we used logistic regression modelling to calculate odds ratios (ORs) for fertility treatments, pregnancy-related conditions and obstetric outcomes.

We found an increased use of fertility drugs in female cancer survivors between 1993 and 2012 compared to siblings (IRR 1.43, 95% confidence interval [CI] 1.25-1.65), which could be explained by the increased use of assisted reproductive technology (IRR 2.41, 95% CI 1.97-2.96). Time period played a key role, with increased use of fertility treatments and assisted reproductive technology in cancer survivors from 2003 onwards (Study I). Female cancer survivors giving birth between 2004 and 2013 had an increased use of fertility treatments compared to siblings (OR 1.84, 95% CI 1.18-2.86) (Study II). Survivors, diagnosed in their childhood, had the lowest use of fertility treatments and seemed to become pregnant with less

extensive fertility treatments than survivors diagnosed as young adults. In cancer survivors giving birth, time elapsed from cancer treatment increased the use of fertility treatments over time, suggesting that cancer treatments lead to a diminished ovarian reserve and a narrowed fertile window (Study II).

One aim for this thesis was to explore the underlying reasons for the previously reported increased risk of preterm delivery. Our results showed that vaginal bleeding and pre-eclampsia might be more severe in cancer survivors, as survivors with these conditions had a 35% higher risk for preterm delivery compared to comparison subjects with the same conditions (Study III). In addition, cancer survivors had an overall increased risk for hospitalization during pregnancy (OR 1.45, 95% CI 1.25-1.68), intrahepatic cholestasis (OR 2.86, 95% CI 1.09-7.49) fear of childbirth (OR 2.25, 95% CI 1.31-3.85) and mental disorders and diseases of the nervous system (OR 5.89, 95% CI 2.31-15.00) (Study III). Cancer survivors also had an increased risk for induction of labor (OR 1.17, 95% CI 1.02-1.35) and elective cesarean sections (OR 1.36, 95% CI 1.11-1.67) compared to siblings. The risk for adverse obstetric outcomes was most increased in childhood cancer survivors (Study IV).

The increased use of fertility treatments in female cancer survivors emphasizes the need for collaboration between oncologists and gynecologists in order to identify those cancer survivors at risk for subfertility or infertility. Our results show an increased use of fertility treatments during recent years, indicating a more active approach towards treating cancer survivors with fertility issues. Our results further indicate that once pregnant, though most cancer survivors have uncomplicated deliveries, some are at an elevated risk for complications, that place them at risk of preterm delivery and adverse obstetric outcomes. Health-care providers should be aware of these risks, attempt to identify these women and provide adequate follow up for this subgroup.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their respective Roman numerals:

I Melin J, Madanat-Harjuoja L, Hirvonen E, Seppä Karri, Malila N, Pitkäniemi J, Gissler M, Tiitinen A. Use of fertility drugs in early onset female cancer survivors – A Finnish register-based study on 8,929 survivors. International Journal of Cancer 2019 Apr; doi: 10.1002/ijc.32346 (in press).

II Melin J, Madanat-Harjuoja L, Heinävaara S, Malila N, Gissler M, Tiitinen A. Fertility treatments among female cancer survivors giving birth – a Finnish register-based study. Acta Oncologica 2017 Aug; 56(8):1089-93.

III Melin J, Heinävaara S, Malila N, Tiitinen A, Gissler M, Madanat-Harjuoja L. Risk factors for preterm delivery among early onset cancer survivors: A Finnish register-based study. International Journal of Cancer 2019 Apr; 144(8):1954-61.

IV Melin J, Heinävaara S, Malila N, Tiitinen A, Gissler M, Madanat-Harjuoja L. Adverse obstetric outcomes among early-onset cancer survivors in Finland. Obstetrics and Gynecology 2015 Oct; 126(4):803-10.

ABBREVIATIONS

AFC	Antral follicle count
ART	Assisted reproductive technology
ATC	Anatomical Therapeutic Chemical
AYA	Adolescents and young adults
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
CPR	Central Population Register
CS	Cesarean section
DM	Diabetes mellitus
DVT	Deep vein thrombosis
ESHRE	European Society of Human Reproduction and Embryology
FCR	Finnish Cancer Register
FET	Frozen embryo transfer
FSH	Follicle stimulating hormone
GDM	Gestational diabetes mellitus
GH	Growth hormone
GnRH	Gonadotropin releasing hormone
HL	Hodgkin lymphoma
HSCT	Hematopoietic stem cell transplantation
ICCC3	International Classification of Childhood Cancer, third edition
ICD-10	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
ICMART	International Committee for Monitoring Assisted Reproductive Technologies
ICSI	Intra cytoplasmic sperm injection
IHC	Intrahepatic cholestasis
IRR	Incidence rate ratio
IVF	In vitro fertilization
IUI	Intrauterine insemination
LMWH	Low molecular weight heparin
LH	Luteinizing hormone
MBR	Medical Birth Register
NHL	Non-Hodgkin lymphoma
OI	Ovulation induction
OR	Odds ratio
PIC	Personal identity code
POI	Premature ovarian insufficiency
PROM	Preterm rupture of the amniotic membranes
RPM	Reimbursement Register for Prescribed Medicines
RR	Relative risk
SII	Social Insurance Institution

SMN	Subsequent malignant neoplasm
STS	Soft tissue sarcomas
TSH	Thyroid stimulating hormone
WHO	World Health Organization

1 INTRODUCTION

According to registry data from recent years, 166 children under the age of 15 years and 1,144 adolescents and young adults, aged 15 to 39 years, are diagnosed with cancer every year (Finnish Cancer Registry Statistics 2012-2016). Fortunately, advances in diagnostics and treatment combinations over the last decades have led to a greater chance of long-term survival for cancer patients than ever before. The five-year survival rate for children diagnosed with cancer in Finland during 2000-2010 was 81% according to a recent study (Madanat-Harjuoja et al. 2014). For adolescents and young adults in Europe, the five-year survival rate was as high as 82% during 2005-2007 (Trama et al. 2016).

However, the same treatments that have led to survival and cure, will lead to adverse health conditions in at least two out of three cancer survivors later in life (Oeffinger et al. 2006). These chronic health conditions can be organ specific, cognitive or hormonal (Hudson et al. 2013). Already in 1975 Giulio D'Angio, a pioneer in the treatment of childhood cancers, was concerned about the possible late effects after cancer treatments (D'Angio et al. 1975). Awareness of these late effects led to an effort to modify and modernize cancer treatments to diminish late complications (Hudson et al. 2011). Recently, effort has also been made to inform health-care providers and cancer survivors about the late effects, to allow early recognition and treatment, and to employ prevention strategies when possible (Hjort et al. 2018, Haupt et al. 2018). A recent development is the Survivorship passport (Surpass), an electronic document that includes a summary of each survivor's clinical history. The Surpass includes information on the primary cancer, received treatments and personalized follow-up and screening recommendations based on the European guidelines (Haupt et al. 2018).

Among cancer survivors, infertility is one of the major concerns and it often leads to distress and interference with intimate relationships thus influencing quality of life (Peate et al. 2009 and Gilleland et al. 2015). Overall, the prevalence of infertility is increasing worldwide and is now estimated to be 12.5-16% of the Western population (Terävä et al. 2008 and Datta et al. 2016). One contributing factor to this increase is believed to be the use of gonadotoxic treatments in cancer patients (Petraglia et al. 2013). As more women postpone childbirth and the number of cancer survivors continues to rise, there is an increasing number of women who desire children after their cancer diagnosis (Canada et al. 2012).

Many studies have demonstrated reduced probability of pregnancy and parenthood in cancer survivors (Madanat et al. 2008, Green et al 2009, Anderson et al 2018). However, only a few studies have been published regarding infertility rates and fertility treatments among cancer survivors (Das et al. 2012, Barton et al. 2013, Luke et al 2016). An American study found that cancer survivors were as likely as their siblings to seek medical help for infertility but less likely to be prescribed fertility drugs (Barton et al 2013). The study did not offer explanations for why reproductive medicine providers prescribed fewer fertility drugs to cancer survivors, indicating a need for more studies on fertility treatments among cancer survivors.

Once pregnant, previous studies have shown that cancer survivors have an increased risk for preterm delivery (Signorello et al. 2006, Madanat-Harjuoja et al. 2010, van der Kooi et al. 2018). The mechanisms underlying this increased risk, however, are unclear. Studies have shown that female survivors who received abdominal radiotherapy have a higher risk for preterm delivery compared to female controls (Green et al. 2010). Reduced vascular supply and uterine fibrosis due to radiotherapy could lead to premature contractions and spontaneous preterm delivery (Critchley et al. 1999). Another explanation could be maternal pregnancy-related conditions that are known to necessitate medically induced preterm delivery. The most common conditions include pre-eclampsia, gestational diabetes and placental pathologies (Ananth et al. 2006). We know that cancer treatments can lead to cardiovascular late effects (Mecham et al. 2010) and increase the risk of metabolic syndrome and diabetes mellitus (Holmqvist et al. 2014). It seems likely that such conditions could appear or worsen during pregnancy and, thus, complicate pregnancies of survivors. Many pregnancy-related conditions, as well as preterm deliveries are associated with an increased risk for medical interventions during pregnancy and labor (Martin et al. 2007), so we also wanted to assess adverse delivery outcomes in cancer survivors. Some studies have reported an increased risk for Cesarean sections, but when it comes to induction of labor and other obstetric outcomes, there are few and partly conflicting reports (Clark et al. 2007, Mueller et al. 2009, Haggar et al. 2014, Reulen et al. 2017).

The studies of this thesis focus not only on fertility treatments but also on pregnancy-related conditions and adverse obstetric outcomes in female cancer survivors. This information can help clinicians to identify cancer survivors requiring fertility counselling or fertility preservation and those at risk for adverse obstetric outcomes. It could also contribute to the development of guidelines for the follow up of pregnancies and management of deliveries in cancer survivors.

2 REVIEW OF THE LITERATURE

2.1 EARLY ONSET CANCER INCIDENCE AND SURVIVAL

2.1.1 CHILDHOOD CANCER

Childhood cancer is defined as cancer diagnosed at the ages of 0-14 years (National Cancer Institute 2018). The incidence rate of childhood cancer has remained stable in Finland (annual standardized incidence rate in 1988-1997 was 173.2 per million) and is higher than Europe´s overall (annual standardized incidence rate of 139.5 per million) (Spix et al. 2006, Madanat et al. 2014). The higher incidence rate in Finland is consistent with rates in the other Nordic countries (Kaatsch et al. 2010) and is believed to be due to the high completeness of registration, though true variations in underlying risk cannot be ruled out (Leinonen et al. 2017).

The current survival rates in Scandinavia are among the highest in the world (80.9% during 1991-2000 in Finland) (Madanat et al. 2014, Gatta et al. 2014). According to the Finnish Cancer Registry data, the most common childhood cancer diagnoses in Finland during 2015 were, in descending order (Figure 1A): leukemia (31.2%), tumors of the central nervous system (CNS) (23.4%) and lymphomas (10.7%) (Engholm et al 2018). Regarding leukemia, the five-year survival rate in Finland in 1991-2002 was higher than in rest of Europe during 1993-1997 (81.5% compared to 77%) (Madanat et al. 2014). The high leukemia survival rates in Finland are the result of a long history of collaboration between the Nordic countries with the aim of standardizing and improving the treatment of childhood leukemia (Coebergh et al. 2006, Madanat et al. 2014). The third most common cancer type among children, lymphomas, are divided into Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). The five-year survival rates for Finnish HL children is 97.2% in the most recent diagnostic period of 2001-2010, whereas the rates are a little lower at 88.7% for NHL children. The survival rate for tumors of the CNS is the lowest of these three most common pediatric malignancies, at 75.4% in the most recent era studied (Madanat et al. 2014).

2.1.2 CANCER IN FEMALE ADOLESCENTS AND YOUNG ADULTS

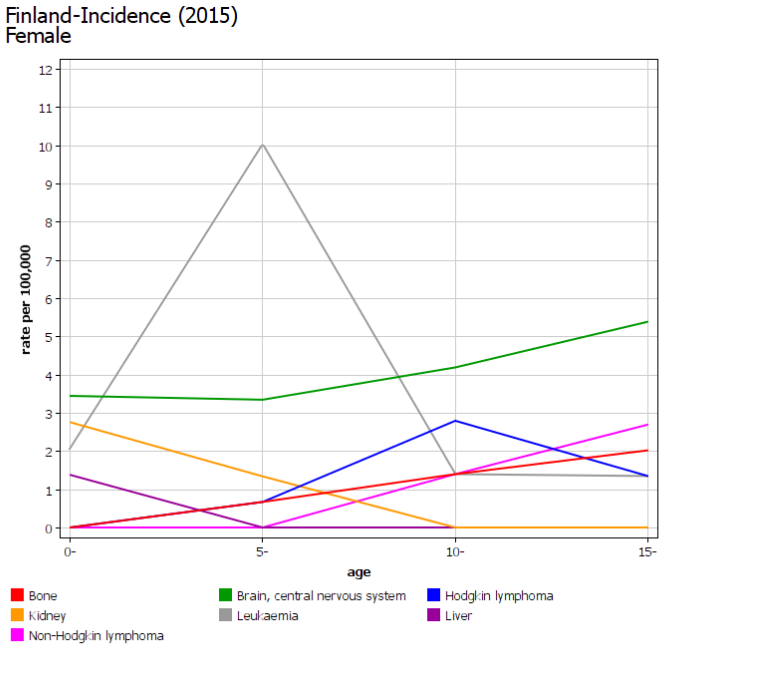
The definition of cancer in adolescence and young adults (AYA) has varied regionally with both 15-19 and 15-39 years age ranges. However, the age range now

accepted by the European Network for Cancer in Children and Adolescents is a cancer diagnosis between 15 and 39 years of age (Desandes 2016). The cancer spectrum shifts towards carcinomas and epithelial neoplasms with increasing age, and typical childhood cancers (such as leukemia and tumors of the CNS) becomes rarer (Ferreira et al. 2013). The studies included in this thesis have, therefore, further subdivided AYAs into those being diagnosed at the ages of 15 to 24 years (adolescents) and those diagnosed at the ages of 25 to 34 or 39 years (young adults).

According to Finnish Cancer Registry data, the most common cancers among female AYAs in Finland during 2015 were, in descending order (Figure 1B): breast cancer (22.9%), cancer of the thyroid (15.2%) and melanoma (15.1%) (Engholm et al. 2018). Attention has been drawn to the fact that adolescents (aged 15-24 years) show poorer survival rates than childhood cancer patients (Gatta et al. 2009). One reason is believed to be delays in diagnosis and cancer treatment (Ofran et al 2014, Ferrari et al 2012). As a result, different initiatives have been undertaken in several European countries with the goal of improving cancer screening methods and collaboration between pediatrics and adult oncologists in specific treatment units (Stark et al 2015). This has led to increasing cancer survival rates among AYAs in Europe, being 79% in 1999-2002 and 82% in 2005-2007 (Trama et al. 2016). The survival rate for Finnish AYAs aged 15-19 years was 83% in 2000-2007 and 91.7% for those aged 20-39 years (Trama et al. 2016). However, in certain leukemias, lymphomas and sarcomas, the survival rates still remain significantly worse in AYAs compared to cancer patients diagnosed in childhood (Trama et al. 2016).

Concerning survival rates (European figures) for the most common cancer types in Finnish female AYAs, patients with breast cancer had a survival rate of 83.5%, cancer of the thyroid a survival rate of 99.2%, and melanomas a survival rate of 88.9% (Trama et al. 2016).

A



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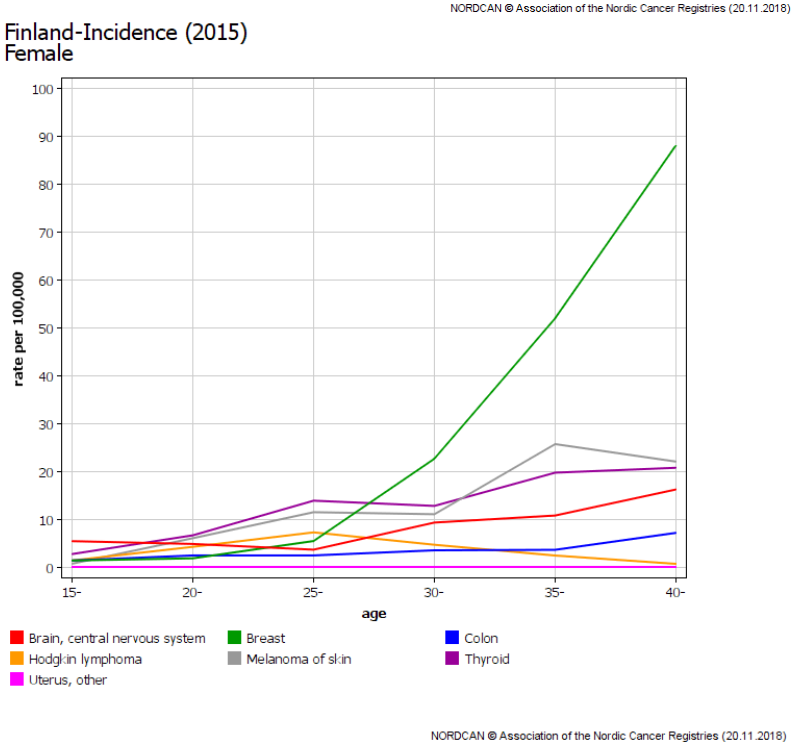

Figure 1. Incidence rates for the 7 most common cancers at the age of 0-14 years (A) and at the age of 15-39 years (B). Published with the permission of NORDCAN (Engholm et al. 2018)

2.2 THERAPIES FOR EARLY ONSET CANCER

Cancer therapies are generally divided into three main modalities: surgical treatment, radiotherapy and chemotherapy. Hematological malignancies are typically managed with combination chemotherapy (Mehta et al. 2011) and solid tumors with surgery, radiotherapy and chemotherapy (Grosfeld et al. 1999). In some cancer types (the most common one being leukemia), myeloablative high-dose chemotherapy, followed by a hematopoietic stem cell transplant (HSCT) may be used in high-risk cases (Passweg et al. 2014). Newer types of treatment include immunotherapy and specific, targeted therapy drugs (Vanneman et al. 2012).

2.2.1 CHILDHOOD CANCER

The notable increase in survival rates after childhood cancer is due to the introduction of chemotherapy in the 1960s (Jones et al. 1987), allowing multi-modality treatment with surgery and radiotherapy. The five-year survival increased as a result from 20-30% in the 1960s (Birch et al. 1988) to over 80% today (Madanat et al. 2014).

When new combinations of cancer treatments, including chemotherapy, became available, the dose and volume of radiotherapy could be gradually decreased or, in some cases, even excluded (Hudson et al. 2012). In one study, 77% of all cancer patients under 21 years of age received radiotherapy during 1970-1979 compared to 33% in 1990-1999 (Turcotte et al. 2017). Another study divided childhood cancer survivors into those receiving cranial irradiation, chest irradiation and abdominal irradiation (Armstrong et al. 2016). This study found that, between the 1970s and 1990s, cranial irradiation among patients with acute lymphoblastic leukemia had decreased from 85% to 19%, chest irradiation among HL patients decreased from 87% to 61% and for abdominal irradiation among Wilms´tumor patients decreased from 78% to 43% (Armstrong et al. 2016). At the same time, progress in radiation technology led to better protection of healthy tissue in cancer patients who still needed radiotherapy (Hudson et al. 2012). This is crucially important, since therapeutic irradiation has been strongly connected with secondary malignancies, pulmonary and cardiac dysfunction and damage to the ovaries (Armstrong et al. 2010, Green et al. 2010). According to a recent study, children diagnosed with cancer in the 1990s had a lower risk for secondary malignancies at 15 years after initial cancer diagnosis compared to those treated in the 1970 (Turcotte et al. 2017). In that study, the lower risk for secondary malignancy was associated with a reduction in the therapeutic radiation dose. Further, Armstrong et al.´s study (2010) observed a reduction in 15-year mortality (from 12.4% to 6.0% between 1970s and 1990s). The

reduction was attributed to the decrease in death from secondary malignancy, cardiac and pulmonary causes (Armstrong et al. 2016).

Chemotherapeutic agents, especially anthracyclins, alkylating agents (divided into classical alkylating agents and platinum-based, alkylating-like agents) and epipodophyllotoxins, have also been associated with an increased risk of secondary malignancies (Kim et al. 2015, Pole et al. 2015). As the use of radiotherapy has decreased, the proportion of survivors receiving anthracyclins, alkylating agents and epipodophyllotoxins is increasing (Turcotte et al. 2017). An increase in the median cumulative dose for epipodophyllotoxins and platinum based alkylating-like agents was observed from 1970-1999, whereas the median cumulative dose for classical alkylating agents and anthracyclins had decreased (Turcotte et al. 2017).

Anthracyclins, which are used in 50-60% of childhood cancer cases (Smith et al. 2010) are known for their cardiotoxic late effects and increased risk for secondary leukemia (Le Deley et al. 2003). Furthermore, alkylating agents are known to cause dose-related gonadal damage. Of these alkylating agents, cyclophosphamide and busulfan, commonly used in childhood cancers (Afify et al. 2000), are considered particularly harmful for the ovaries (Morgan et al. 2012). Epipodophyllotoxins have been associated with an increased risk for secondary acute myelogenous leukemia (Le Deley et al. 2003).

2.2.2 CANCER IN ADOLESCENTS AND YOUNG ADULTS

AYA patients have been referred to as “the lost tribe” since less attention has been given to this cancer group compared to childhood cancer patients and adult cancer patients (Fernandez et al. 2006). Malignant epithelial neoplasms become more common (breast cancer, thyroid cancer and melanoma) in AYAs and surgical treatment usually plays a bigger role than in childhood cancer patients (Bleyer et al. 2009). The cancers in AYAs have been shown to have a different biology and pathogenesis than cancers in children and adults, probably explaining the poorer survival rates for some cancers among AYAs (Trama et al. 2016). Diagnosis and treatment tailored to the specific histopathologic cancer types might improve the survival rates (Bleyer et al. 2008).

AYAs with breast cancer (the most common cancer type in female AYAs) generally have poorer survival rates than older adults, as the breast cancer typically has a more aggressive phenotype (Keegan et al. 2012). Although general principles for using chemotherapy and targeted agents are the same for breast cancer in AYAs and older

adults, use of endocrine therapy varies in pre- and postmenopausal women (Tichy et al. 2013). Approximately 60% of breast cancers diagnosed under the age of 50 years are estrogen receptor positive diseases (Anderson et al. 2002). The standard care for estrogen receptor positive breast cancers is adjuvant endocrine therapy with tamoxifen for at least five years. Suppression of ovarian estrogen production (by administering luteinizing hormone-releasing hormone agonists), oophorectomy or ovarian ablation in premenopausal women have yielded conflicting results and more studies are needed (Theriault et al. 2013, Smyth et al. 2015).

The overall survival rate for thyroid cancer (99.2%) is one of the highest among all types of cancers in AYAs (Trama et al. 2016). Based on an American study (Hay et al 2017), most AYAs with thyroid cancer are treated similarly to adult thyroid cancer patients, even though recent guidelines suggest a more conservative approach with less complications (Francis et al. 2015). Two different approaches are available for AYAs: radical treatment or a more conservative approach (Massimino et al. 2018). The radical treatment includes total thyroidectomy and lymphadenectomy (in cases of lymph-node metastases), followed by radioactive iodine treatment. Common postoperative complications after radical surgery include hypoparathyroidism (Massimino et al. 2006) and recurrent laryngeal nerve palsy (Sosa et al. 2008). Late effects after radioactive iodine treatment include infertility, salivary gland dysfunction and an increased risk for secondary malignancy (Lee et al. 2010). This therapy should only be used in high-risk patients, taking the possible late effects into account (Francis et al. 2015, Massimino et al. 2018). A more conservative approach, removing only the affected thyroid lobe and only the lymph node with metastases, is often recommended for AYAs (Collini et al. 2006). A recent study concluded that individual treatment that takes the clinical presentation and histopathologic type of the thyroid cancer into account is recommended (Spinelli et al. 2016).

Melanoma is the third most common cancer, accounting for 15.1% of all cancers in female AYAs in Finland (Engholm et al. 2018). The incidence of melanoma is increasing, especially in female AYAs (Davar et al. 2016). It is estimated that 75% of all melanomas diagnosed in subjects under 30 years of age are due to exposure to natural or artificial sunlight (Sender et al. 2015). Education on sun safety and skin self-examination are vital, especially since it is difficult to change the health behaviors of AYAs (Sender et al. 2015). As melanomas in AYAs are genetically similar to those of adults, the treatment is also the same, although more attention is needed on psychosocial support and encouragement to participate in clinical trials (Davar et al. 2016).

The survival rates are worse in AYAs compared to childhood patients for certain leukemias, lymphomas and sarcomas, (Trama et al. 2016). Special treating units with a multidisciplinary team have been suggested to improve survival rates for AYAs that will, hopefully, increase the cooperation between pediatric and adult oncologists and increase the likelihood of participation in clinical trials (Stark et al. 2015).

2.3 LATE EFFECTS OF CANCER AND ITS TREATMENT

Late effects of cancer are defined as health problems that occur months or years after the cancer treatment has ended (National Cancer Institute 2018). Often used synonyms are adverse events and late sequelae. Adverse events are defined as unfavorable and unintended events with abnormal clinical findings that are associated with the use of cancer treatment (National Cancer Institute 2018). This term is used for both acute and chronic complications, often in the context of management of chemotherapy administration and dosing and in clinical trials (National Cancer Institute 2018). Late sequelae of cancer is defined as a chronic, pathological condition often resulting from the primary disease/injury (Oxford Dictionary 2018). In this thesis, the term "late effects of cancer" includes both adverse events and late sequelae of cancer.

According to different studies (Armstrong et al. 2014, Hudson et al. 2013, Bhakta et al. 2017), 60% to 90% of all cancer survivors will have at least one or more chronic, health-related conditions later in life. By the age of 50 years, 50% of the childhood cancer survivors have experienced a late effect that is categorized as severe, disabling, or life-threatening morbidity or death compared to 20% of their siblings (Armstrong et al. 2014). Factors related to the cancer type and cancer treatment can, to some extent, predict the risk for late effects in cancer survivors (National Cancer Institute 2018). However, for an individual cancer patient, host-related factors should also be taken into account when assessing the risk for late effects (National Cancer Institute 2018). Figure 2 describes these factors in more detail.

2.3.1 SECONDARY MALIGNANCIES

Subsequent malignant neoplasms (SMNs) are defined as histologically distinct neoplasms occurring at least two months after the treatment of the primary cancer has ended (National Cancer Institute 2018). SMNs are the most common reasons for non-relapse, late mortality in cancer survivors. A recent study showed that 58% of all deaths occurring five years or more after initial cancer diagnosis, are due to SMNs (Mertens et al. 2008). A Nordic study on cancer survivors diagnosed under 19 years

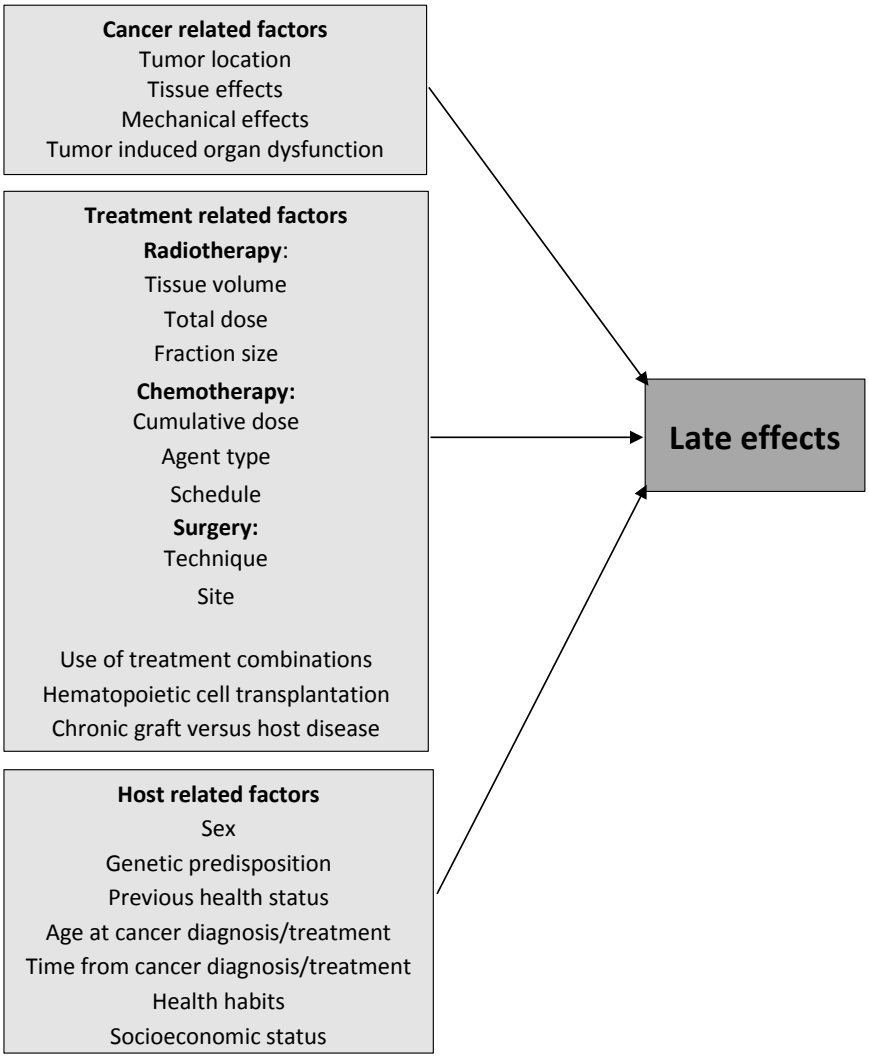

Figure 2 Factors that should be considered when assessing the risks for late effects of cancer and its treatments (National Cancer Institute 2018)

of age (Olsen et al. 2009) found a 3.3-fold increased risk of SMNs compared to the general population. Sex and age at cancer diagnosis are risk factors for SMNs. According to one study, women had a higher risk for SMN compared to men, probably explained by secondary breast cancer (Friedman et al. 2010). The most common SMNs in females were breast cancer, thyroid cancer, non-melanoma skin cancer and meningioma (Friedman et al. 2010). Age at primary cancer diagnosis has been found to be an important risk factor, as children under 10 years of age have an increased risk for meningioma, malignant CNS tumors, sarcomas, and thyroid cancers

(Neglia et al. 2001). Breast cancer, non-melanoma skin cancer, and other solid organ cancers (including head and neck, small intestine, and colorectal cancers) were the most common ones in survivors aged 15-21 years at cancer diagnosis (Friedman et al. 2010). Treatment-related risk factors for secondary malignancies included exposure to radiotherapy, as well as treatment with high doses of anthracyclins, alkylating agents and epipodophyllotoxins (Mertens et al. 2008, Pole et al. 2015). SMNs due to chemotherapy are characterized by a short latency, meaning that the increased risk for SMN is observed during a limited time period, with a peak time of between three to nine years from treatment (Blayney et al. 1987). Instead, there is generally a long latency of two to three decades for SMNs due to radiotherapy (Metayer et al 2000).

2.3.2 CARDIOVASCULAR LATE EFFECTS

Cardiovascular disease, is the third most common cause of late mortality in childhood and AYA cancer survivors, after SMNs and pulmonary morbidity (Kremer et al. 2001, Mertens et al 2008). According to a Finnish study (Kero et al. 2014), cancer survivors diagnosed below 35 years of age had an increased risk for cardiomyopathy, atherosclerosis, cardiac ischemia and cardiac arrhythmia. Treatment-related factors associated with an increased risk for cardiovascular late effects are certain chemotherapies, including anthracyclins, alkylating agents, antimetabolites and anti-microtubule agents (Simbre et al. 2005) as well as radiotherapy (Swerdlow et al. 2007). According to two studies (Aleman et al 2007, van der Pal et al 2012), the combination of mediastinal radiotherapy and anthracyclins was associated with the highest risk for cardiovascular late effects. Among survivors exposed to cardiac-directed radiotherapy, 56.4% experienced cardiac late effects in the form of mild to moderate heart valve abnormalities (Hudson et al. 2013).

Cardiotoxicity can be divided into early toxicity, usually appearing within hours to weeks but less than a year from cancer treatment, and late toxicity, which occurs more than a year from cancer treatment, usually 10-20 years later (Koutsoukis et al. 2018). Risk factors for cardiovascular late effects included early toxicity, higher dose of anthracyclins and mediastinal radiotherapy, young age at cancer diagnosis, increasing time since cancer treatment and female sex (Armstrong et al. 2007). According to one study (Krischer et al 1997), female cancer survivors treated with anthracyclins have an almost two-fold increased risk for sudden death, congestive heart failure or cardiotoxicity compared to male cancer survivors. In Green et al.´s study (2001), female Wilms` tumor survivors have a 4.5-fold increased risk of being treated with digoxin or diuretics for congestive heart failure compared to male

cancer survivors. It is recommended that cancer survivors with an increased risk for cardiomyopathy and congestive heart failure undergo surveillance starting two years after the completion of cardiotoxic therapy and continuing every five years thereafter (Armenian et al. 2015).

2.3.3 METABOLIC SYNDROME AND GASTROINTESTINAL LATE EFFECTS

The National Cholesterol Education Program has defined metabolic syndrome as the presence of three or more of the following components: increased waist circumference, elevated triglycerides, reduced HDL-Cholesterol, elevated blood pressure and elevated fasting glucose (Alexander et al. 2003). Metabolic syndrome is associated with an increased risk for type 2 diabetes mellitus (DM) and atherosclerotic disease (Eckel et al. 2005).

Early onset cancer survivors treated with cranial radiotherapy and total body irradiation in combination with chemotherapy have an increased risk for metabolic syndrome (Taskinen et al. 2007, van Waas et al. 2010, Nottage et al. 2014). A study on survivors with hematologic malignancies (Trimis et al. 2007) showed that cranial radiotherapy is associated with the highest risk for metabolic syndrome. In that study, 22% of survivors treated with a combination of cranial radiotherapy and chemotherapy were found to have metabolic syndrome, whereas only 8% of those being treated with chemotherapy alone suffered from it (Trimis et al. 2007). Another study comprising 500 childhood cancer survivors found that total cholesterol levels and systolic blood pressure were higher in female cancer survivors compared to healthy female controls (van Waas et al. 2010). This study also found an increased risk for obesity among cancer survivors treated with cranial radiotherapy (van Waas et al. 2010). A study of childhood acute lymphoblastic leukemia survivors, who were treated with cranial radiotherapy found a more than 2.5-fold increased risk for obesity compared to siblings (Oeffinger et al. 2003). A threefold higher risk of infertility has been shown in obese women compared to non-obese women (Wise et al. 2010). Furthermore, overweight is associated with negative outcomes for women undergoing IVF, due to poor oocyte quality and lower preimplantation (Bellver et al. 2010).

Two studies on DM (type 1 and 2 combined) found a 1.6-1.8-fold increased risk in cancer survivors compared to siblings or the general population (Mecham et al. 2009, Holmqvist et al. 2014). The increased risk is associated with total body irradiation, abdominal irradiation and alkylating agents, as well as younger age (0-4 years) at diagnosis (Mecham et al. 2009). Leukemia, neuroblastoma, germ-cell and CNS

neoplasms, Hodgkin`s lymphoma, as well as malignant bone and Wilms´ tumor, are associated with an increased risk for DM (Mecham et al 2009, Holmqvist et al. 2014, Gunn et al. 2015).

Concerning gastrointestinal late effects and liver diseases, a Scandinavian study found a 60% higher risk for these outcomes in cancer survivors compared to the general population (Asdahl et al. 2016). Survivors of hepatic tumors, neuroblastomas and leukemia have the highest excess risk for gastrointestinal late effects and liver diseases (Asdahl et al. 2016). Specific late effects that are increased among cancer survivors include constipation, which has a big impact on quality of life, and liver cirrhosis, which increases the mortality. Another study (Goldsby et al. 2011) found similar results but in addition, the risk for colostomy/ileostomy and liver biopsy was increased.

2.3.4 LATE EFFECTS OF THE ENDOCRINE SYSTEM

According to a recent study, 48% of all childhood cancer survivors will suffer from endocrine late effects, and the risk generally increases with time from the cancer diagnosis (Brignardello et al. 2013). Endocrine late effects in females can be divided into those resulting from damage to the hypothalamic and/or pituitary gland (including deficiency of growth hormone, gonadotropins, thyrotropins and corticotropins) and damage affecting the peripheral organs (ovaries, thyroid and adrenal glands) (Constine et al. 1993). Damages to the ovaries (primary hypogonadism) will be covered in a separate section.

Cranial radiotherapy affects the hypothalamic, pituitary and thyroid gland negatively (Nandagopal et al. 2008, Chemaitilly et al. 2015). According to a recent study on childhood cancer survivors treated with cranial radiotherapy (Chemaitilly et al. 2015), 46.5% suffered from growth hormone deficiency, 10.8% from central hypogonadism and 7.5% from thyrotropin deficiency. Similar results are found in a Scandinavian study (de Fine Licht et al. 2014), in which childhood cancer survivors have a 4.8-fold increased risk of a hospital contact for endocrine disorders. In that study, pituitary hypofunction is the most common disorder, followed by hypothyroidism and dysfunction of the gonads. The risk is highest among leukemia survivors and those treated for CNS tumors (de Fine Licht et al. 2014). HSCT also increases the risks for several endocrine disorders in cancer survivors (including poor growth, hypogonadism, hypothyroidism and osteopenia), especially since it is often carried out in combination with total body irradiation (Nandagopal et al. 2008). Overall, the risk for endocrine late effects after chemotherapy are considered less

common compared to those after radiotherapy, with the exception of ovarian dysfunction (Nandagopal et al. 2008).

Cranial radiotherapy, which can lead to central hypogonadism, can appear as arrested puberty, pubertal delay or symptoms of decreased sex hormone production depending on age and pubertal status at time of treatment (Meistricht et al. 1997, Chemaitilly et al. 2015). In small radiation doses, gonadotropin deficiency can occur after several years. However, with cranial radiotherapy at a dose of more than 35G, up to 20% will experience symptoms of gonadotropin deficiency within 10 years post-treatment (Armstrong et al. 2009). Childhood cancer survivors have an increased risk for hypothyroidism, which is dependent on the cancer type (Madanat et al. 2008, Brignardello et al. 2013). Childhood cancer survivors of thyroid cancer, CNS tumor and HD, have the highest risk for hypothyroidism, probably because the radiation field included the thyroid (Madanat et al. 2008).

2.3.5 NEUROCOGNITIVE LATE EFFECTS

Neurocognitive and psychological late effects can occur as intellectual decline, memory loss, attention deficit and behavioral problems (Kadan-Lottick et al. 2010). It is often difficult, however, to separate neurocognitive late effects due to cancer treatment from other psychosocial factors related to every day life as a cancer patient, such as the hospital environment, missing out on school and lack of social stimulation (Brown et al. 1993). According to one study (Nandagopal et al. 2008) almost 50% of all childhood cancer survivors had neurocognitive problems. Cancer survivors who were treated with cranial radiotherapy have been reported to have the highest risk for neurocognitive late effects, although the risk is also increased after intrathecal chemotherapy and systematic therapy, especially with high-dose methotrexate or cytarabine (Nathan et al. 2007, Wefel et al. 2008). Patients with acute lymphoblastic leukemia and brain tumors have the highest risk for neurocognitive late effects (Nathan et al. 2007). Other risk factors are female sex and younger age at cancer diagnosis (Khan et al. 2015, Ellenberg et al. 2009). According to a Finnish study, female cancer survivors receiving cranial irradiation and chemotherapy below the age of seven years have poorer school performance compared to controls (Harila-Saari et al. 2007).

2.3.6 PSYCHOSOCIAL LATE EFFECTS

The majority of early onset cancer survivors report a reduced quality of life, which is believed to be partially due to different late effects (Yeh et al. 2016). Reports on

psychological distress and other mental health problems are partly conflicting. In three studies, survivors who have undergone cranial radiotherapy (van der Geest et al. 2013), brain surgery (Vuotto et al. 2017), as well as those treated with anthracyclins (Sun et al. 2011), have an increased risk for mental health problems. In general, cancer survivors reporting pain and worsening health status also had an increased risk for anxiety and depression (Brinkman et al. 2013). Another study found mental health problems in cancer survivors treated with anthracyclins to be connected to cardiovascular late effects (Spewak et al 2017). Regarding host-related factors, an increased risk for psychological stress is related to female gender, lower education, unemployment and unmarried status (Zeltzer et al. 2008).

Two studies report higher rates of psychological distress and psychosocial problems among cancer survivors diagnosed as adolescents compared to childhood cancer survivors (Mody et al. 2008, Krull et al. 2010). According to a third study, adolescents are particularly challenged socially, and the cancer diagnosis and treatment sometimes interferes with detachment from parents (Johannsdottir et al. 2010). Krull et al.´s study (2010) found that adolescents, aged 12-17 years, have an increased risk for attention deficit disorders and emotional problems compared to siblings (Krull et al. 2010).

Most studies found no increased risk for depression in cancer survivors (Parslow et al. 2000, Kazak et al. 2010, Yeh et al. 2016). In many studies, however, outcomes are evaluated based on hospital data, thus missing the less severe (but probably more common) cases treated in primary care (Parslow et al. 2000). Cancer survivors in an American study reported medication use for anxiety and depression at rates nearly two times those reported by the general population (Hawkins et al. 2017). A Norwegian study found a 19% higher use of antidepressants in cancer survivors diagnosed below the age of 25 years compared to age-matched controls. The risk was highest for survivors of CNS tumors and leukemia (Johansdottir et al. 2017).

2.3.7 LATE EFFECTS ON THE FEMALE REPRODUCTIVE SYSTEM

2.3.7.1 The ovaries

In addition to gonadotropin secretion-related damage (central hypogonadism), cancer survivors are also at risk of gonadal dysfunction related to the ovaries (primary hypogonadism) (Sklar et al. 1999). Abdominal radiotherapy, as well as HSCT and chemotherapy with alkylating agents, can damage the ovaries (Wallace et al. 1989,

Chemaitilly et al. 2006, Vatanen et al. 2014). The ovaries of prepubertal girls are generally considered more resistant to damage from chemotherapy and radiotherapy compared to adult women´s ovaries (Meistricht et al. 1997). When ovarian failure occurs before puberty onset, it will result in delayed puberty and primary amenorrhea. If ovarian failure occurs after puberty, it will cause secondary amenorrhea and/or menopausal symptoms (Meistricht et al. 1997, Webber et al. 2016). Ovarian insufficiency is often the reason for infertility in cancer survivors (Webber et al. 2016, Levine et al. 2018).

The loss of ovarian function within five years after cancer treatment is referred to as acute ovarian failure (Chemaitilly et al. 2006). If the ovaries cease to function many years after cancer treatment but before the age of 40 years, the term premature menopause or premature ovarian insufficiency (POI) is used (Byrne et al. 1999, Webber et al. 2016). Thus, the presence of apparently normal ovarian function at the completion of cancer treatment does not rule out ovarian damage. According to a study (Chemaitilly et al. 2006) on childhood cancer survivors, 6.3% developed acute ovarian failure after cancer treatment. The risk seemed to increase with advancing age at cancer diagnosis and more than half of the survivors with acute ovarian failure had received ovarian irradiation of at least 10 Gy (Chemaitilly et al. 2006). A recent study on premature menopause (Levine et al. 2018) found that the prevalence of non-surgical premature menopause in cancer survivors at the age of 40 years was 9.1% and the risk compared to siblings was more than ten-fold.

2.3.7.2 The uterus

Cancer treatments, especially abdominal radiotherapy, have been shown to damage the uterus (Beneventi et al. 2015). In one study, childhood cancer survivors who received abdominal radiotherapy had an up to 40 % smaller uterine volume, compared to those who received chemotherapy (Larsen et al. 2004). Another study found reduced uterine blood flow and uterine fibrosis among adult cancer survivors treated with radiotherapy before puberty (Critchley et al. 1999). Researchers believed for many years that chemotherapy had little or no impact on uterine function (Nicholson et al. 1993). A recent study, however, shows that busulfan in combination with bone marrow transplantation increases the risk of uterine damage (Beneventi et al. 2015). The data are limited on the effect of chemotherapy alone on the uterus. Uterine damage due to cancer treatment often develops slowly, so the risk for late effects increases with a woman´s advancing age (Beneventi et al. 2015). The risk of uterine damage as a consequence of abdominal radiotherapy and chemotherapy has also been found to increase in a dose dependent manner (Green et al. 2010).

2.4 PARENTHOOD IN CANCER SURVIVORS

Europe is the continent with the most rapid fall in fertility rates (Lutz et al. 2006). The fertility rate in Finland decreased for the eighth year in a row in 2018, at 1.40 births per woman (Statistics Finland 2018) (Figure 3). Explanations for the declining fertility rates in Europe are complex and differs among countries (Gauthier et al. 2007). Generally, the number of couples not having children and those having fewer children have increased during recent years, as well as the number of couples delaying childbirth beyond the period of subfertility (The ESHRE Capri Workshop Group 2010).

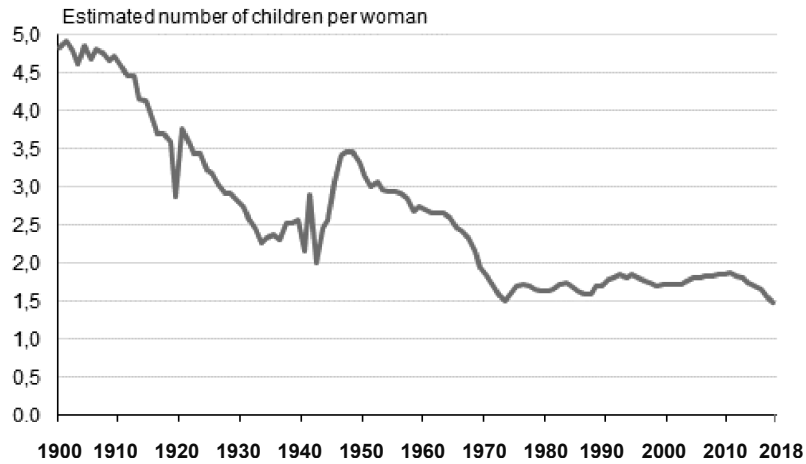

Figure 3 Total fertility rate in Finland during 1900 to 2018. Modified from Statistics Finland (2019)

The probability of early onset cancer survivors marrying and/or having children post-diagnosis is reduced by up to 50% compared to their siblings and the general population (Madanat et al. 2008, Pivetta et al. 2011). The reduced probability for parenthood is most likely not only due to reduced pregnancy rates; cancer survivors and their spouses are less motivated to have children because of the experienced cancer (Oosterhuis et al. 2008). Studies based on questionnaire data have found that the desire to have children is lower in childhood cancer survivors than in the general population (Reinmuth et al. 2008). Cancer survivors are concerned about the health of future offspring and the recurrence of their own cancer. They are also worried about educational and financial setbacks as an effect of the cancer treatment and have expressed difficulties in finding a partner and conceiving (Reinmuth et al. 2008). According to one study, female cancer survivors living in a relationship have a 1.8-fold increased risk for divorce/separation compared to healthy controls (Kirschhoff

et al. 2012). Generally, however, experiencing cancer increases the value placed on family and the importance of parenthood (Langeveld et al. 2002, Schover et al. 2002). According to one survey (Mancini et al. 2011), no association existed between motivation to have children and cancer type, age of the patient or time elapsed from cancer diagnosis.

As more women decide to delay childbirth, the risk increases for receiving a cancer diagnosis before the family is complete (Nabukera et al. 2006, Canada et al. 2012). A rapid increase in the survival rates of early onset cancer patients has led to changing attitudes towards parenthood and childbearing among cancer survivors and health-care providers (Peccatori et al. 2013). Historically, especially female breast cancer survivors were discouraged from having children (Holleb et al. 1965). It was believed that high levels of ovarian estrogens and progestins, pituitary prolactin and placental hormones during pregnancy could affect possible microscopic tumor tissue in the body and lead to a recurrence of cancer (Holleb et al. 1965). Nowadays, pregnancies after cancer are considered safe, and cancer survivors should not be discouraged from having children after their cancer treatment (Peccatori et al. 2013). A meta-analysis of 14 retrospective control-studies even found a 41% lower risk of death among female breast cancer survivors who conceived when compared to those who did not (Azim et al. 2011).

There are no standard recommendations concerning the ideal time interval between cancer treatment and pregnancy (Lambertini et al. 2016). Two aspects should be considered: firstly, the biological effects of the anticancer treatment on the body of the mother should be sufficiently small to not harm the development of the fetus; secondly, the interval should be long enough to minimize the risk for cancer relapse (Lambertini et al. 2016). Individual timing based on the risk of relapse, age of the woman and ovarian reserve is recommended (Peccatori et al. 2013). A time interval of two years following cancer diagnosis is generally recommended for breast cancer patients (Peccatori et al. 2013). Adjuvant tamoxifen treatment for at least five years after diagnosis is recommended in estrogen receptor positive breast cancer patients. Insufficient data exists to date to support the safe interruption of tamoxifen and attempting pregnancy before the five-year treatment period is completed (Lambertini et al. 2016). One study that compared estrogen receptor positive breast cancer survivors who became pregnant to those who did not, found no difference in the disease-free interval (Azim et al. 2013). Furthermore, when comparing estrogen receptor positive survivors who became pregnant within two years of cancer diagnosis to those who became pregnant later, no difference was found in the disease-free interval (Azim et al. 2013). However, the study lacked statistical power to address the safety of early tamoxifen interruption (Azim et al. 2013).

2.5 FERTILITY IN CANCER SURVIVORS

2.5.1 SUBFERTILITY AND INFERTILITY

The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) defines infertility as "a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person´s capacity to reproduce either as an individual or with his/her partner" (Zegers-Hochschild et al. 2017). Couples with a high probability of conception will often conceive within one to four cycles, whereas a couple with low probability of conception may need many cycles of trying (Wilcox et al. 1988). These couples are often referred to as subfertile (reduced in their chances of conceiving compared to other couples). Couples with no chance of conceiving are sterile. Many subfertile couples seeking help for infertility could probably conceive without medical treatment if they would only try longer (Taylor et al. 2003).

The prevalence of infertility is increasing worldwide and is now estimated to be 13-16% among the Western population (Terävä et al. 2008, Datta et al. 2016). Self reported lifetime subfertility in Finland is 16% (Terävä et al. 2008). The reasons for the increasing prevalence of infertility are numerous and vary in different parts of the world (Datta et al. 2016). Lifestyle and nutritional factors, infections due to sexually transmitted diseases and post-abortion complications are believed to play a central role (Mascarenhas et al. 2012 and Petraglia et al. 2013). Delaying childbearing until later in life, exposure to chronic stress and environmental pollutants as well as gonadotoxic cancer treatments damaging the reproductive system, play a larger role in western countries (Petraglia et al. 2013).

According to ICMART, the most common causes of female infertility can be divided into ovulatory disorders (including ovulatory disturbances and diminished ovarian reserve), tubal factors, endometriosis, uterine/cervical factors and unexplained infertility (Figure 4) (Zegers-Hochschild et al. 2017). According to a systematic review from the United Kingdom (Bhattacharya et al. 2010), 10-20% of all infertility cases are unexplained. Ovulatory disorders accounted for 27%, tubal factors for 14%, endometriosis for 5% and low sperm count or quality for 19% of the infertility cases.

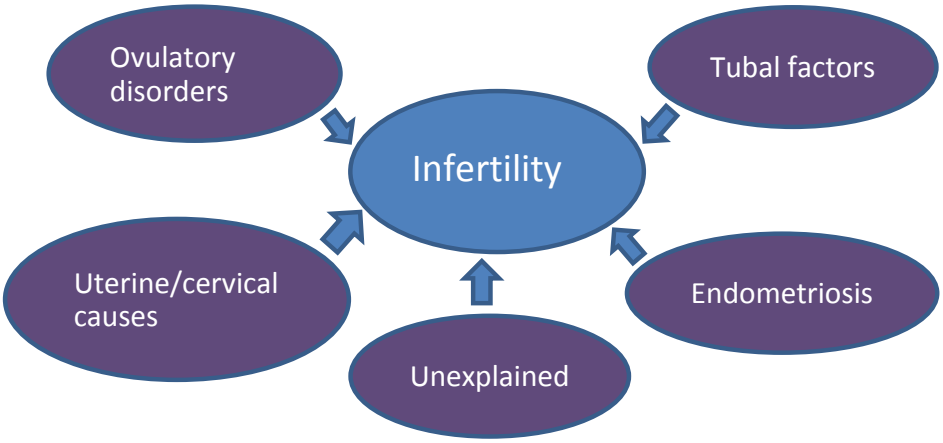

Figure 4 Different causes for female infertility (Zegers-Hochschild et al. 2017)

Many studies have shown that cancer survivors have decreased rates for parenthood, pregnancy and live birth compared to siblings or the general population (Table 1). The potential fertility issues are a big concern among cancer survivors and parents of childhood cancer survivors (Taylor et al. 2016). However, pregnancy rates vary based on cancer type, according to a Norwegian study (Stensheim et al. 2011). As an example, treatment of melanoma or thyroid cancer do not decrease pregnancy rates compared to controls, whereas survivors of leukemia, cervical and breast cancer have the lowest pregnancy rates (Stensheim et al. 2011). In one study (Green et al. 2009) hypothalamic/pituitary irradiation of more than 30 Gy, as well as radiation doses of more than 5 Gy on the ovaries, decreases the possibility of ever becoming pregnant in cancer survivors. Use of alkylating agents was also associated with lower pregnancy rates in cancer survivors (Green et al. 2009).

Parenthood and pregnancy rates are indirect measurements of the potential harm caused by cancer and its treatments on the reproductive system, as other factors will also affect the likelihood of becoming pregnant and a parent (the wish to have children and finding a partner, to name a few) (van Dorp et al. 2018). Gonadal function is a more direct measurement when estimating subfertility or infertility caused by cancer treatments; although similar to pregnancy rates, it does not take into account the actual wish for a pregnancy or whether there was an attempt to become pregnant. Gonadal injury can manifest as POI and infertility (Anderson et al. 2015). In one study (Sklar et al. 2006), comprising 2819 cancer survivors and 1065 female siblings, the cumulative incidence for non-surgical POI was 8% among cancer survivors and 0.8% among their siblings. The incidence was almost 30% for cancer survivors treated with both alkylating agents and abdominal radiotherapy. In addition to increasing doses of radiation or chemotherapy, a high age at diagnosis is

associated with a higher risk for POI (Sklar et al 2006). According to a recent study (Levine et al. 2018) cancer survivors who developed nonsurgical, premature menopause are less likely to become pregnant (RR 0.49, 95% CI 0.27-0.80) or have a live birth (RR 0.42, 95% CI 0.19-0.79) between the age of 31 to 40 years compared to survivors without premature menopause. It is important to remember, however, that a woman´s fertility will decrease several years before menopause (Barton et al. 2013); therefore, a regular menstruation cycle cannot rule out infertility in cancer survivors.

When assessing the risk for POI, in addition to detection of menstrual cycle and FSH serum levels, measurement of antral follicle count (AFC) and anti-Mullerian hormone (AMH) is often used (Anderson et al. 2013, Dunlop et al. 2015, Freour et al. 2017). Measurement of AFC requires a vaginal ultra-sound, performed early in the follicular phase by a skilled operator, whereas AMH serum levels can be measured at any time during the menstrual cycle (Freour et al. 2017). AMH is produced by growing ovarian follicles and is considered a good tool to measure ovarian reserve (Dunlop et al. 2015). A low AMH serum level can predict POI in adult women many years before actual menopause, but AMH can also be used to predict treatment-related ovarian damage in prepubertal childhood cancer survivors (Dunlop et al. 2015). AMH is also used to predict ovarian reserve and expected ovarian response before fertility treatments, especially in women of a higher age (Rasool et al. 2017). However, one study (Hagen et al. 2013) found that young, healthy women with low AMH levels had a similar time to pregnancy compared to those with normal AMH. Another study (Hamre et al. 2012) on female childhood cancer survivors found that although 44% of the cancer survivors had low AMH levels, 93% achieved pregnancy. AMH is currently considered a good tool to measure ovarian reserve, but further studies are needed to predicting the need for fertility treatments or fertility preservation in cancer survivors (Freour et al. 2017). Studies have shown measurement of AFC and AMH to be equally good markers on ovarian reserve (Freour et al. 2017). However, AMH serum levels are easier to measure than AFC, thus, it is more frequently used (Freour et al. 2017).

Table 1 Overview of the largest cancer survivor studies on parenthood, pregnancy and live birth rates

Study	Cancer diagnosis	Age at diagnosis	End of follow-up	Cohort size	Reference group	Outcome	Rates (95% CI)
Childhood, adolescent and young adult cancer survivors in Finland (Madanat et al. 2008)	1953-2004	<35 years	31.12.2006	11,320	Siblings	Parenthood	0.46 (0.44-0.48)
Childhood cancer survivor study (Green et al. 2009)	1970-1986	<21 years	1.11.2000	5,149	Siblings	Pregnancy rate	0.81 (0.73-0.90)
Cancer Registry and the Medical Birth Registry of Norway (Stensheim et al. 2011)	1967-2004	16-45 years	31.12.2006	16,105	Matched, general population	Pregnancy rate	0.61 (0.58-0.64)
The Italian AIEOP Off-Therapy Registry (Pivetta et al. 2011)	1960-1998	<15 years	30.10.2006	2,670	Matched, general population	Live births	0.57 (0.53-0.62)
Childhood and adolescent cancer survivors in Sweden (Armuand et al. 2017)	Born 1973-1977	<21 years	31.12.2012	552	Matched, general population	Live births	0.79 (before 1988) 0.71 (after 1988)
Scottish Cancer Registry (Anderson et al. 2018)	1981-2012	<40 years	31.12.2014	23,201	General population	Pregnancy rate	0.62 (0.60-0.63)

2.5.2 FERTILITY TREATMENTS

A clinical fertility assessment is generally recommended in the absence of any known cause of infertility if a couple have tried to conceive over one year (National Institute for Health and Care Excellence 2013). An earlier assessment is recommended if a woman is over 35 years of age or a known cause of infertility is present. Persons at risk of infertility because of a planned treatment (cancer treatment for example) should be offered immediate referral to a specialist (National Institute for Health and Care Excellence 2013).

According to the International Glossary on Infertility and Fertility Care, medically assisted reproduction (MAR) includes ovulation induction, ovarian stimulation, all assisted reproductive technologies (ART), uterine transplantation and intrauterine, intracervical and intravaginal insemination with semen of husband/partner or donor (Zegers-Hochschild et al. 2017). Ovulation induction (OI) is generally used in anovulation or oligo-ovulation with the aim to induce normal ovulatory cycles. The most commonly used drugs are clomiphene citrate, aromatase inhibitors and gonadotropins. Ovarian stimulation aims to induce the development of ovarian follicles and can be followed by timed intercourse or insemination, as well as ART, to obtain multiple oocytes at follicular aspiration. Intrauterine insemination (IUI) is a procedure in which laboratory-processed sperm is injected into the uterus to attempt a pregnancy. The most common reason for use of IUI is low semen quality, but it is also used in unexplained infertility. ART includes all interventions requiring in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction. This includes, but is not limited to, in vitro fertilization (IVF), intra-cytoplasmic sperm injection (ICSI), frozen embryo transfer (FET), embryo and oocyte cryopreservation or donation (International Glossary on Infertility and Fertility Care).

With regard to fertility treatments, only a few studies exist that document these outcomes in cancer survivors. Barton et al.´s study (2013) found a 48% increased risk for clinical infertility in cancer survivors compared to controls. Cancer survivors sought medical help for their infertility as often as their siblings but were less likely to be prescribed fertility drugs for their condition (RR 0.57, 95% CI 0.46-9.70). Despite a longer time to pregnancy among cancer survivors with clinical infertility, nearly two-thirds of cancer survivors with infertility reported a pregnancy (Barton et al. 2013).

Another study (Das et al. 2012) estimated the ovarian reserve and response to IVF and in vitro maturation treatment following chemotherapy. They found that female cancer survivors have lower peak estradiol levels on the day of human chorionic gonadotropin administration during fertility treatments and a lower number of oocytes that can be retrieved compared to healthy female controls. A third study (Luke et al. 2016) investigated the likelihood of a live birth in cancer survivors using autologous oocytes or donor oocytes. They found that live birth rates after the use of donor oocytes are similar compared to healthy controls, whereas live birth rates after use of autologous oocytes decrease in cancer survivors compared to controls.

Only a few published studies, mostly on breast cancer patients, are available concerning the safety of fertility treatments and controlled ovarian stimulation after cancer (Meirow et al. 2014, Oktay et al. 2015, Goldrat et al. 2015). Short-term exposure of high estrogen levels in ovarian stimulation during ART is a concern in breast cancer survivors, especially those with endocrine receptor positive tumors (Meirow et al. 2014). Overall survival rates and relapse of cancer were similar in breast cancer patients undergoing ART compared to breast cancer patients without fertility treatments (Goldrat et al. 2015). In the study by Goldrat et al., however, most fertility treatments were oocyte donations and ovulation inductions, procedures requiring no or very low hormonal ovarian stimulation. To avoid high estrogen levels during ART, alternative protocols for ovarian stimulation with co-administration of tamoxifen or letrozole have been developed (Meirow et al. 2014, Oktay et al. 2015). Pregnancy rates with these alternative protocols are similar to those of healthy women undergoing ART in these studies (Oktay 2015). To summarize, current limited data suggest that fertility treatments and controlled ovarian stimulation do not increase the risk for cancer recurrence (Lambertini et al. 2016).

2.5.3 FERTILITY PRESERVATION

ICMART defines fertility preservation as various interventions, procedures and technologies to preserve reproductive capacity (Zegers-Hochschild et al. 2017). A fertility preservation procedure can be performed before medical treatment that may cause infertility (such as radiotherapy or chemotherapy) or after cancer treatment, if diminished ovarian reserve is detected in a cancer survivor not ready to attempt pregnancy (National Cancer Institute 2018). Different fertility preservation options are available based on patient-related factors and cancer-treatment related factors. These factors include the woman´s age, whether the woman has a partner,

possibility to postpone cancer treatment, type of cancer treatment and the risk of metastasis to the ovaries (Roberts et al. 2005).

Embryo and oocyte cryopreservation are the main methods of preserving fertility in female cancer patients (Peccatori et al. 2013). These are established fertility preservation methods that require the woman to go through oocyte retrieval, after which the embryo or oocyte is cryopreserved (Oktay et al. 2018). The success rate depends on the number and quality of follicles retrieved. Pregnancy rates were previously higher with embryo cryopreservation compared to oocyte cryopreservation (Kuwayama et al. 2005). However, during recent years, the pregnancy rates after oocyte cryopreservation have improved with results similar to those of embryo cryopreservation (Rienzi et al. 2012). The major limitation of these techniques is the delay in cancer treatment (typically 10-14 days) (Lambertini et al. 2016). Embryo cryopreservation requires a partner or sperm donor, whereas oocyte cryopreservation can be performed on single women. These treatment methods can, however, only be used in post-pubertal women.

In ovarian tissue cryopreservation, ovarian cortical tissue is obtained by surgery (laparoscopy or laparotomy), dissected into small fragments and cryopreserved (Ronn et al. 2014). After cancer treatment, the tissue can be re-transplanted into the pelvis or abdominal wall (Ronn et al. 2014). This technique has proven to be effective but it is still experimental, in contrast to embryo and oocyte cryopreservation (Loren et al. 2013, Anderson et al. 2015). It can be used in prepubertal girls and in adult women who cannot delay cancer treatment or who have already received cancer treatment (Lambertini et al. 2016). One concern with this technique is the potential reintroduction of cancer cells, especially in hematological malignancies (Lambertini et al. 2016). There is ongoing research on in vitro techniques that would make it possible to develop mature oocytes from the primordial follicle stage. This would enable use of cryopreserved ovarian tissue for later IVF instead of re-transplantation of ovarian tissue (Bertoldo et al. 2018, Fabbri et al. 2018).

In addition to these, there are a number of other techniques that have been used with variable success (Ronn et al. 2013). Ovarian suppression with gonadotropin-releasing hormone (GnRH) agonist treatment during chemotherapy as a method to maintain fertility has yielded conflicting results (Oktay et al. 2018). However, recent studies (Moore et al. 2015, Lambertini et al. 2015) have shown a protective effect on the ovaries, and one meta-analysis of breast cancer patients found a reduced risk of 64% of treatment-related POI and an increasing possibility of 83% for pregnancy (Lambertini et al. 2015). The current recommendation is that ovarian suppression can be considered if other fertility preservation techniques are not feasible (Oktay et

al. 2018). Ovarian transposition (oophoropexy) indicates a surgical procedure in which the ovaries are moved out of the radiation field to protect the ovarian function in cancer patients (Lee et al. 2006). Its success rate is approximately 50% based on short-term menstrual function (Clough et al. 1996). However, menstrual function is a poor measurement of fertility and it is possible that the success rate is lower. Scatter radiation and reduced ovarian blood supply are believed to be the most common reasons for failure (Clough et al. 1996). One concern is the possibility of metastatic disease in the ovaries. In Morice et al.´s (2000) study of women with cervical cancer, a metastatic disease was found in a minority (1%) of the patients after ovarian transposition.

International guidelines of fertility preservation in cancer patients (Lambertini et al. 2016, Oktay et al. 2018) recommend that clinicians should discuss the impact of cancer treatments on fertility with all cancer patients or their parents as early as possible. Furthermore, fertility preservation should be considered if the patient is interested in having children later on. In Finland, different cancer treatments have been categorized according to the risk of permanent amenorrhea (Table 2). Table 2 is a modification of the original categorization by the American Society of Clinical Oncology (Lee et al. 2006). Cancer treatments with an over 80% risk for permanent amenorrhea are classified as having a very high risk for infertility, whereas treatments with a less than 20% risk for amenorrhea are classified as having a low risk for infertility. Treatment combinations, new cytotoxic drugs and individual reactions to treatments pose a challenge when evaluating the risk for infertility (Lee et al 2006). In Finland, fertility preservation for prepubertal girls with cancer is considered if the risk for infertility is very high, whereas for post-pubertal girls and adult women it is considered if the risk for infertility is high (Finnish National Recommendations for Fertility Preservation 2019).

Table 2 Risk of infertility according to the main cancer treatments. A modification of the original categorization by American Society of Clinical Oncology (Lee et al 2006).

Cancer treatment		Low risk	Intermediate risk	High risk	Very high risk	No data
Radiation	Ovaries			<10 Gy	>10 Gy	
	Spine		18-24 Gy	24-36 Gy		
	Abdomen		10-15Gy pre pub	>15 Gy pre pub		
			5-10 Gy post pub	>10 Gy post-pub		
	Uterus		14-30 Gy	>25 Gy pre pub >45 Gy post pub		
	Vagina		90-100 Gy			
	Total body			X		
HSC					X	
Classical alkylating agencies	Cyclophos-phamide		<6-9 g/m^2	>6-9 g/m^2		
	Busulfan			600 mg/m^2		
	Melphalan					X
	Chlorambucil					X
	Ifosfamide		<10 g/m^2	>10 g/m^2		X
	Procarbazine			X		
	Carmustine			X		X
	Lomustine		<360 mg/m^2	>360mg/m^2		X
Platinum-based alkylating agencies	Cisplatin		X			
	Carboplatin		X			
Anti-metabolites	Methotrexate	X				
	Mercaptopurine	X				
	5-fluorouracil	X				
Vinka-alkaloids	Vincristine	X				
	Vinblastine	X				
Podofyllotoxine	Asparginase	X				
Anti-tumour antibiotics	Bleomycin	X				
	Dactinomycin	X				

HSCT= Hematopoietic stem cell transplantation, Gy=Gray

2.6 PREGNANCY IN CANCER SURVIVORS

An increasing number of women around the world are postponing their pregnancy to later in life (United Nations. World fertility patterns 2015). The average age of primiparas in Finland was 26.5 years in 1987 and 29.2 years in 2017 (Statistics Finland 2017). Similar trends have been reported elsewhere in developed countries (Matthews et al. 2014). Women older than 40 years of age have a higher risk of chromosomal abnormalities in offspring, miscarriage and preterm delivery than younger women (Fredriksen et al. 2018). Maternal obesity is also rapidly increasing in the western world (Hansson et al. 2016). In Finland, every third pregnant woman is overweight (defined as a BMI over 25 kg/m^2), and 13% are obese (defined as a BMI over 30 kg/m^2) (Rönö et al. 2014). Overweight women have an increased risk for gestational diabetes mellitus (GDM) and pre-eclampsia as well as an increased risk for cesarean section (CS) and postpartum infections (Athukorala et al. 2010). These two factors are a challenge for obstetricians today.

Preterm delivery is defined as a delivery before week 37 of gestation. In Europe, 75% of all neonatal deaths occur in infants born preterm (Chang et al. 2013). Incidence rates for preterm delivery vary among the European countries, representing 5-10% of all live births (Chang et al. 2013). Preterm deliveries can be sub-classified into two groups: spontaneous preterm deliveries and preterm deliveries due to maternal pregnancy-related conditions, necessitating medically induced preterm delivery (Goldenberg et al. 2008, Menon et al. 2010). Many studies have consistently showed that the risk for preterm delivery is elevated among cancer survivors compared to siblings and healthy controls (Table 3); however, the reasons behind the preterm deliveries are unclear. Some studies have found the risk to be associated with abdominal radiotherapy (Green et al. 2010, Signorello et al. 2006). In childhood and adolescent cancer patients, abdominal irradiation could lead to a reduced uterine volume and blood flow (Larsen et al. 2004), resulting in uterine fibrosis and cervical shortening. This, in turn, could lead to premature contractions and rupture of the amniotic membranes during pregnancy, both of which are risk factors for spontaneous preterm delivery (Menon et al. 2010). However, chemotherapy has also been associated with preterm delivery (Madanat-Harjuoja et al. 2010, Anderson et al, 2017). Here, a different mechanism must be responsible. One explanation could be maternal pregnancy-related conditions that might necessitate medically induced preterm deliveries. The most common conditions are pre-eclampsia, GDM and placental pathologies (Ananth et al. 2006).

Regarding possible conditions that explain spontaneous preterm delivery in cancer survivors, only a few studies are available, and those mostly studied

premature rupture of the amniotic membranes (Clark et al. 2007, Reulen et al. 2017, Haggar et al. 2014); one included threatened preterm labor (Haggar et al. 2014). None of these studies found an increased risk for either of these outcomes. Concerning maternal pregnancy-related conditions, that could possibly lead to medically induced preterm delivery in cancer survivors, an Australian study (Haggar et al. 2014) found an increased risk for pre-eclampsia (RR 1.32, 95% CI 1.04–1.87) and GDM (RR 2.65, 2.08–3.57). These results were confirmed in a British study (Reulen et al. 2017) in which survivors of Wilms tumor treated with abdominal radiotherapy had over a threefold risk for the development of hypertension (RR 3.29, 2.29-4.71) and GDM (RR 3.35, 1.41-7.93) during pregnancy. Only one study (Haggar et al. 2014) on placental pathology in cancer survivors was found, which showed no increased risk for retained placenta. Placental pathologies increase the risk not only for postpartum hemorrhage, one of the leading causes for maternal mortality, but also preterm delivery (Campbell et al. 2006), making it an important target to study. Green et al.´s study (2010) evaluated the occurrence of malpresentation of the fetus (a common reason for elective CS) and found that the risk for malpresentation of the fetus increased with increasing dose of abdominal radiation.

Cancer survivors, especially those treated with anthracyclins or chest irradiation, have an increased risk of cardiac abnormality later in life (Lipshultz et al. 2006, Armenian et al. 2015). The physical stress of a pregnancy could trigger cardiomyopathy or pulmonary hypertension, originally caused by the cancer treatment (Lipshultz 2006). Hines et al.´s retrospective cohort study (2016) evaluated pregnancy-associated cardiomyopathy and found that cardiomyopathy occurred rarely (0.3%) in pregnant cancer survivors, but an increased risk was observed among those treated with anthracyclins. Accordingly, surveillance for cardiomyopathy is recommended before pregnancy or during the first trimester for all cancer survivors who have been treated with anthracyclins or chest irradiation (Armenian et al. 2015).

Table 3 Overview of the largest cancer survivor studies on pregnancy and obstetric outcomes. An upward arrow indicates an increased risk.

Study	Cancer diagnosis	Age at diagnosis	End of follow-up	Live births of survivors	Reference group	Outcomes
Childhood Cancer Survivor Study (Signorello et al. 2006)	1970-1986	<21	1.11.2002	2,201	Siblings	Preterm delivery↑ low birth weight↑
The Scottish Cancer Registry (Clark et al.2007)	n.m.	n.m.	2005	1,122	General population	Preterm delivery↑, pre-eclampsia, PPH↑, induction, CS↑, etc
National Cancer Institute (Mueller et al. 2009)	1973-2000	<20	2001	1,898	Matched, general population	Preterm delivery↑, weight<2500g↑, GDM, pre-eclampsia, anemia, CS etc.
Childhood, adolescent and young adult cancer survivors in Finland (Madanat-Harjuoja et al. 2010)	1953-2004	<35	31.12.2006	1,309	Siblings	Preterm delivery↑, low birth weight↑
Western Australia Cancer Registry (Haggar et al. 2014)	1982-2007	15-39	31.12.2008	1,894	Matched, general population	Threatened preterm birth, GDM↑, pre-eclampsia↑, retained placenta, CS↑, etc.
The North Carolina Central Cancer Registry (Anderson et al. 2017)	2000-2013	15-39	31.12.2014	2,598	Matched, general population	Preterm delivery↑, low birth weight↑ CS↑, etc.
The British Childhood Cancer Survivor Study (Reulen et al. 2017)	1940-1991	<15	31.12.2012	2,783	General population	GDM, Pre-eclampsia, CS↑, PPH, PROM, Malpresentation, etc.
The Scottish Cancer Registry (van der Kooi et al.2018)	1981-2012	<40	31.12.2014	1,629	Matched, general population	Preterm delivery↑, low birth weight, PPH↑, assisted vaginal birth, CS↑, breech

2.7 DELIVERY IN CANCER SURVIVORS

Cesarean section (CS) rates are increasing worldwide. Awareness has been raised during the last decade about the risks that accompany CS, and attempts have been made to decrease these rates (WHO statement on cesarean section rates 2015). A CS can be life-saving in certain medical indications, such as in pre-eclampsia, placenta praevia, transverse lie of the fetus or asphyxia of the fetus (Hannah et al. 2000). However, the main reason for the increased CS rates is believed to be CS being performed without medical reasons on the mother´s request (Betran et al. 2018). The WHO has recommended a CS rate between 10 and 15%, based on CS rates in countries with the lowest maternal and perinatal mortality rate (Betran et al. 2015). The CS rate in Finland was 16.7% in 2017 (Statistics Finland 2017), which is low compared to other developed countries. Insufficient data exists on why certain women would opt for CS without a medical reason (Betran et al. 2018). Fear of childbirth (Nieminen et al. 2017), need for control and cultural acceptance regarding CS might play a role (Betran et al. 2018). Potential risk factors associated with CS include intrapartum and postpartum hemorrhage of the mother, infections and problems in subsequent pregnancies (including placental pathologies and uterine scar rupture) (Boerma et al. 2018). Differences in neonatal physiology following vaginal delivery and CS delivery are also believed to have a negative effect on the fetus after CS (Betran et al. 2018).

Rates of induction of labor are increasing in the western world, ranging from 20% to 30% (Zeitlin et al. 2013). The most common indication for induction of labor is post-term pregnancies (more than 41 weeks of gestational age), where induction of labor has been shown to decrease perinatal mortality (Gulmezoglu et al. 2012). Induction of labor is also used in maternal pregnancy-related conditions that necessitate delivery (pre-eclampsia, GDM, premature rupture of the amniotic membranes, to name a few) or in fetal-related conditions (growth restriction or intrapartum infections) (Boulvain et al. 2001). However, the decision to induce a labor should be carefully considered as some studies indicate that induction of labor is associated with an increased risk for CS by up to 37% (Vrouenraets et al. 2005, Kruit et al. 2015).

Many studies have evaluated the risk for CS in cancer survivors. All except one (Table 3) show an elevated risk for CS in general or elective CS with RRs of 1.1-2.6. One study (van der Kooi et al. 2018), however, observed that in survivors with a more recent cancer diagnosis, the risk for CS approached rates in controls. Two studies (Clark et al. 2007, van der Kooi et al. 2018) evaluated the risk for assisted vaginal delivery

(breech delivery or delivery with vacuum extraction/forceps) and found a small but significant increased risk in cancer survivors compared to female controls. Conflicting results are reported regarding the risk of postpartum hemorrhage in cancer survivors. Some studies found no increased risk (Haggar et al. 2014, Reulen et al. 2017), whereas one study (van der Kooi et al. 2018) found an overall increased risk (RR 1.42, 1.29–1.55), that, however, approached rates in controls during the most recent time period. Only one study on induction of labor was found (Clark et al. 2007) with no elevated risk.

3 AIMS OF THE STUDY

This study focused on the reproductive health of female early onset cancer survivors by using registry data. The present investigation assessed fertility treatments, pregnancy-related conditions and adverse obstetric outcomes in this group of survivors. The following specific aims were addressed:

1. To study the use of fertility drugs in female cancer survivors.

2. To identify the associations of cancer characteristics and fertility treatments in female cancer survivors giving birth.

3. To identify pregnancy-related conditions and risk factors for preterm delivery in female cancer survivors.

4. To study adverse obstetric outcomes and operative deliveries in female cancer survivors.

4 MATERIALS AND METHODS

This study was based on a cohort of Finnish female cancer survivors diagnosed with cancer between 1953 and 2004 at the age of 0-34 years (Study II and IV) and cancer survivors diagnosed between 1953 and 2012 at the age of 0-39 years (Study I and III).

4.1 REGISTERS

4.1.1 THE CENTRAL POPULATION REGISTER (CPR)

Since 1967, each person being born or permanently living in Finland is assigned a personal identity code (PIC) that allows individual linkage between different registers and databases. The Central Population Register (CPR), founded in 1969, is nationwide and covers all Finnish residents. The CPR includes basic personal information (such as PIC, name, address, residential history, family relations, death or emigration). Individuals born in 1955 or later can reliably be linked to their parents, and offspring. While all children of a parent are listed, siblings of cancer survivors can be identified.

4.1.2 THE FINNISH CANCER REGISTRY (FCR)

The nationwide Finnish Cancer Registry (FCR), founded in 1952, began registration one year later, in 1953. In 1961, the National Board of Health made it compulsory to report all cancer cases diagnosed in the Finnish health-care system. The clinical information is usually reported by the physician treating the patient and the histologic data by the department of pathology. In addition to these, Statistics Finland reports information on death certificates concerning malignancies directly to FCR. Thus, the data in this nationwide cancer register covers 96% of solid tumors and 86% of hematologic malignancies. Of all cancers, 93% were morphologically verified (Leinonen et al. 2017). According to tumor behavior, cancer cases are divided into four different groups: benign, semi-malignant, in-situ and invasive cancers. All benign and semi-malignant tumors, except those of the central nervous system (CNS), were excluded in this thesis. Benign and semi-malignant CNS tumors were included, as their treatment is similar to that of malignant CNS tumors. This thesis also excluded in-situ cancers. Other data recorded in the FCR include anatomical site, histology, treatment (radiotherapy, chemotherapy, surgery and hormonal) and time of diagnosis.

4.1.3 THE MEDICAL BIRTH REGISTER (MBR)

The Medical Birth Register (MBR) was established in 1987 and contains information on nearly all live births and stillbirths with a birth weight of more than 500g or a pregnancy duration of at least 22 weeks. Data is compiled at the delivery hospital, using the maternity records. Missing information is completed by using data compiled by the Population Register Center and Statistics Finland that provide information on births outside the hospital, as well as stillbirths and deaths during the first week of life (Gissler et al. 2004). This way, less than 0.1% of infants are missing from the MBR (Gissler et al. 2002). In addition, the MBR contains detailed information on pregnancy-related conditions. Reforms of the MBR were made during 1990 and 2004, both times adding more important outcomes to follow. ICD-10 diagnostic codes from the maternity records are included in the MBR from 2004 onwards.

4.1.4 REIMBURSEMENT REGISTER FOR PRESCRIBED MEDICINES (RPM)

Study I investigated fertility treatments in female cancer survivors and their siblings based on fertility drug prescription. That study used information from the Reimbursement Register for Prescribed Medicines (RPM), in addition to previously mentioned studies. The RPM is controlled by the Social Insurance Institution (SII) and started to register purchased prescription drugs in 1993. The register is complete from 1995 onwards and includes all purchased, reimbursed prescription drugs. Over-the-counter drugs and drugs received in hospital care are not included. This database includes the patients´ PIC, drug substance, purchase date, amount delivered, package size and price of the medication. Drugs are coded according to the specific categories of the Anatomical Therapeutic Chemical (ATC) codes released by the WHO. A study comparing data on fertility drug purchase from RPM and aggregated IVF statistics in Finland found a good coverage in this register (Gissler et al. 2004).

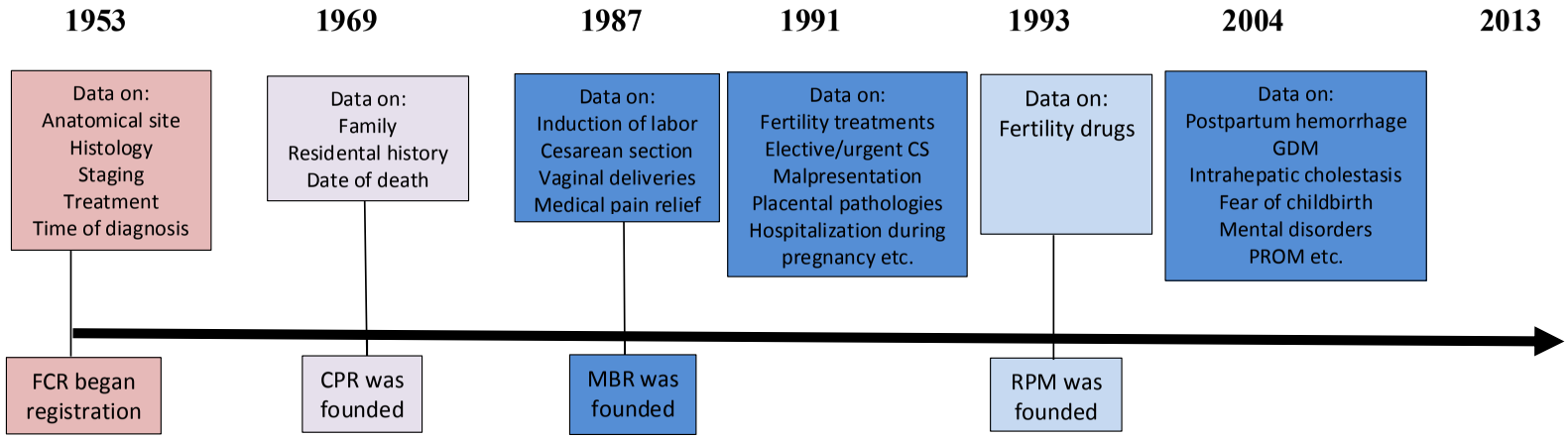

Figure 5 Timeline from 1953 to 2013 showing the registers used and outcomes measured in the different studies
FCR = Finnish Cancer Registry, CPR = Central Population Register, MBR = Medical Birth Register, RPM=Reimbursement Register for Prescribed Medicines

4.2 STUDY POPULATION

This thesis evaluated three different female cancer patients/survivors cohorts (Table 4). Cancer survivors were compared to half and full siblings in three of the studies (Studies I, II, IV). Study III compared cancer survivors to five age-matched female comparison subjects per case.

4.2.1 STUDY I

Study I identified 23,125 female cancer survivors from the FCR who were diagnosed with cancer between January 1953 and December 2012, at 0-39 years of age (Figure 6). The study identified 20,542 female siblings without cancer before 16 years of age by linkage to the CPR. It identified 16,640 survivors and 18,184 siblings without deliveries before possible drug purchase between 1993 and 2012 by further linkage to MBR and RPM. The study included only women who were in the age range of 16-41 years between 1993 and 2012, wich left us with 8,929 survivors and their 9,495 siblings. The fertility drug purchase was the primary outcome during this time period and age range, whereas pregnancies greater than 22 gestational weeks, death, emigration or cancer diagnosis in the sibling-group were secondary outcomes. Those with a notification of aromatase inhibitor medication as a long-term cancer treatment (used in breast cancer) were excluded from the follow up. Altogether, the follow-up time was 48,638 person years for survivors and 56,102 person years for siblings.

Table 4 Description of data obtained from the different outcome registers for studies I-IV. FCR= Finnish cancer register, CPR= Central population register, MBR= Medical Birth Register, RPM= Reimbursement register for prescribed medicines

Study	Cancer diagnosis	Study cohort	Reference cohort	Registers	Outcome	Time period
I	1953-2012 (0-39 years)	23,125	Siblings 20,542	FCR, CPR, MBR, RPM	Use of fertility drugs	1993-2012
II	1953-2004 (0-34 years)	13,799	Siblings 21,640	FCR, CPR, MBR	Fertility treatments	2004-2013
III	1953-2012 (0-39 years)	24,610	Matched controls 121,353	FCR, CPR, MBR	Pregnancy-related outcomes	1991-2013
IV	1953-2004 (0-34 years)	13,799	Siblings 21,640	FCR, CPR, MBR,	Obstetric outcomes	1987-2013

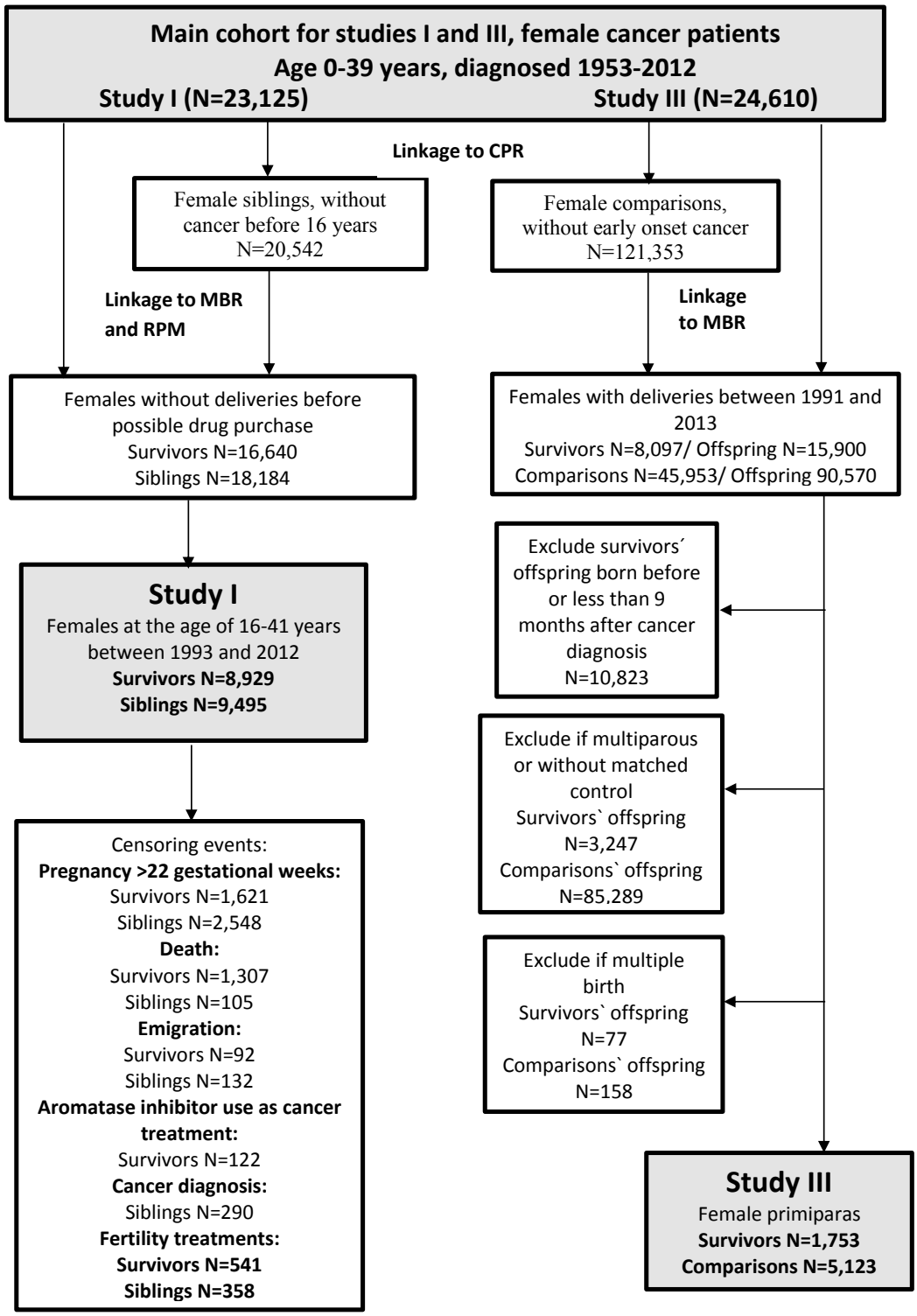

Figure 6 Characteristics of data collection for Study I and Study III

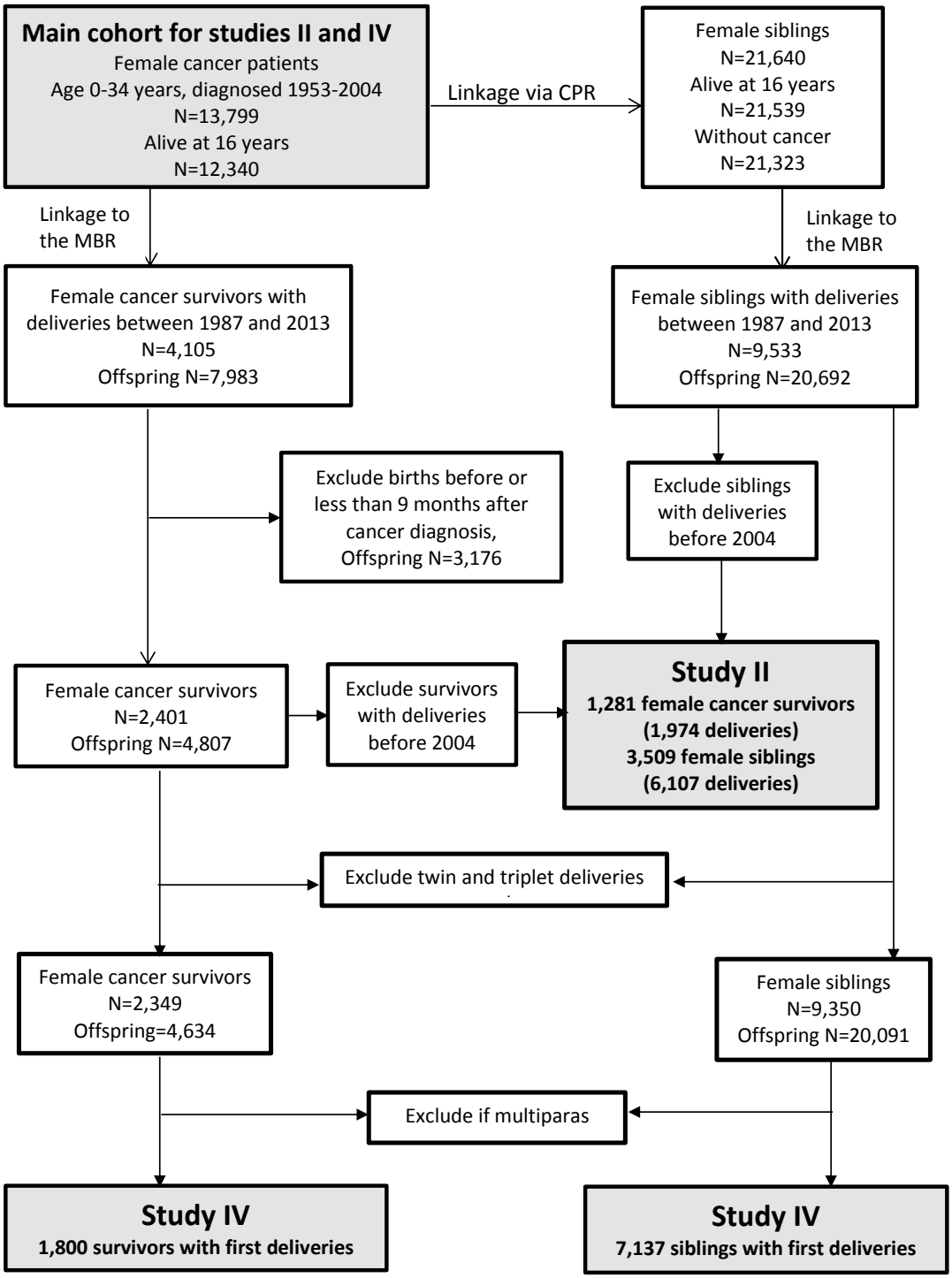

Figure 7 Characteristics of data collection for Study II and Study IV

4.2.2 STUDIES II AND IV

We identified 13,799 female cancer patients from the FCR, diagnosed between January 1953 and December 2004 at 0-34 years of age (Figure 7). We used the PIC to identify 21,323 siblings of cancer patients from the CPR. By linking these two cohorts to the MBR, we identified 2,401 cancer survivors (excluding those who were pregnant during cancer treatment) and 9,533 siblings with deliveries between January 1987 and December 2013. Information on overall fertility treatments were available from January 1991 onwards and the fertility treatments were even further sub-categorized from January 2004 onwards. As we wanted to evaluate different types of fertility treatments in Study II, we excluded women giving birth before January 2004, which left us with 1,281 survivors with 1,974 deliveries and 3,509 siblings with 6,107 deliveries. We also present new, unpublished results in this thesis on fertility treatments among cancer survivors and their siblings giving birth between January 1991 and December 2013 (2,230 survivors with 4.282 deliveries and 8,185 siblings with 16,787 deliveries).

Study IV used the same study population as in Study II, with some exceptions; only first, singleton pregnancies were included but for a longer time period, between 1987 and 2013, than in Study II (Figure 7). This left us with 1,800 deliveries of cancer survivors and 7,137 deliveries of siblings.

4.2.3 STUDY III

We identified 24,610 female cancer patients alive at 16 years of age from the FCR. These cancer patients were diagnosed between January 1953 and December 2012, at 0-39 years of age (Figure 6). We sampled five age-matched female comparison subjects for every cancer patient. We received information about pregnancy-related conditions, as well as the deliveries, by linking these two cohorts to the MBR. This study also excluded deliveries occurring before or less than 9 months after cancer diagnosis (10,823 deliveries). We wanted to avoid the possible influence that a previous pregnancy history or a multiple birth might have on the outcomes studied, so we included only first, singleton pregnancies in this study. Altogether, 1,753 survivors and their 5,123 matched comparisons were included in this study.

4.3 METHODS

In all our studies, cancer survivors were sub-categorized according to cancer type based on the International Classification of Childhood Cancer (ICCC3) (Steliarova-Foucher et al. 2005), primary cancer treatment, time from diagnosis to fertility drug purchase/delivery and diagnostic age (Table 5). In addition, Study I used information on calendar time period at possible fertility drug purchase and attained age of the women. Studies II, III and IV used information on maternal age at delivery, maternal smoking, gestational age and year of delivery (Table 6). The follow up for cancer survivors, siblings and comparison controls started from 16 years of age in all our studies.

Table 5 Diagnostic characteristics used in this thesis

Cancer characteristics				
Age at diagnosis (years)	0-14 (childhood)			
	15-24 (adolescents)			
	25(-34)-39 (young adults)			
Cancer treatment	Chemotherapy			
	Radiotherapy			
	Surgery, only			
	Missing			
Cancer type (ICCC3)	Leukemia			
	Lymphoma			
	CNS			
	Sympathetic Nervous System			
	Retinoblastoma			
	Renal Tumors			
	Hepatic Tumors			
	Malignant bone Tumors			
	Soft tissue and other Sarcomas			
	Germ cell, Gonadal and Trophoblastic neoplasms			
	Carcinomas and other malignant epithelial neoplasms			
	Others			
Time from diagnosis to fertility drug purchase/delivery (years)	**Study I**	**Study II**	**Study III**	**Study IV**
	0-2	0-5	0-5	0-1
	3-5	6-10	6-10	2-5
	6-10	11-15	11-38	6-10
	11-41	16-25		11-34
		26-34		

Table 6 Descriptive characteristics of the women, used in this thesis

Study I			
Calendar time period	1993-1997		
	1998-2002		
	2003-2007		
	2008-2012		
Attained age (years)	16-19		
	20-24		
	25-29		
	30-34		
	35-41		
Studies II-IV			
Time period of delivery	**Study II**	**Study III**	**Study IV**
	2004-2008	1991-2002	1987-1989
	2009-2013	2003-2013	1990-1999
			2000-2009
			2010-2013
Age at delivery (years)	<25		
	25-29		
	30-34		
	35 or more		
Maternal smoking	No		
	Yes		
	Missing		
Infant sex	Male		
	Female		
Gestational age	<32 (very preterm delivery)		
	32-36 (preterm delivery)		
	37-41 (full term delivery)		
	42 or more (post term delivery)		
	Missing		
Birth weight (g)	<1500		
	1500-2499		
	2500-3999		
	4000-4499		
	4500 or more		

4.3.1 STUDY I

To identify fertility treatments in female cancer survivors and their siblings, we performed a linkage to the RPM. Fertility drugs prescribed to these women during 1993-2012 were analyzed and used as a proxy for use of fertility treatments. The main outcome was overall fertility treatment, which was further sub-classified into

OI (including IUI) and ART (including in vitro fertilization, intracytoplasmic sperm injection and frozen embryo transfer).

We used information on fertility drug purchases during the following 21 days after the initial fertility drug purchase to sub-classify fertility treatments as either OI or ART. A fertility treatment was classified as an OI if clomiphene citrate or an aromatase inhibitor alone was used without the combination of any other fertility drug during the following 21 days. The treatment was also classified as an OI if a gonadotropin was used without use of GnRH analogues. A fertility treatment was classified as an ART if a GnRH agonist or GnRH antagonist was the first drug used. Gonadotropin use in combination with GnRH analogues was also classified as ART. In this data, four survivors were excluded from the follow up after a notification of fertility drug purchase but before being categorized into the OI or ART treatment group. Two siblings were included in the follow up after categorization into the any treatment group but before categorization into the OI or ART treatment group (as their matched survivor received a cancer diagnosis after the sibling's initial fertility drug purchase). This explains why the numbers in the OI and ART treatment groups do not always add up to the numbers in the any treatment group (Table 8).

4.3.2 STUDY II

To investigate fertility treatments in cancer survivors and siblings leading to delivery, we gathered information on fertility treatments from the MBR. In the MBR, information on fertility treatments is based on self-report of the mother and her maternity records. Overall fertility treatments are available from 1991 onwards and sub-classified into OI (including IUI) and ART (including IVF, ICSI and FET). IUI is reported as a separate group from 2004 onwards, enabling classification of fertility treatments into three sub-groups: OI, IUI and ART.

4.3.3 STUDY III

Study III compared maternal pregnancy-related conditions in cancer survivors and matched comparison subjects. Pregnancy-related outcomes found in the MBR were either available since 1991 (any hospitalization, which was subclassified into hospitalization due to threatened preterm labor, vaginal bleeding and pre-eclampsia, as well as malpresentation and placental pathologies) or 2004 (premature rupture of the amniotic membranes, use of low molecular weight heparin (LMWH) for prevention of deep vein thrombosis (DVT), GDM, intrahepatic cholestasis (IHC), fear

of childbirth, diseases of the circulatory system and mental disorders and diseases of the nervous system complicating pregnancy and childbirth). In this study, some of the outcomes were based on dichotomous variables (hospitalization due to different reasons, use of LMWH and GDM), whereas others were based on ICD-10 codes: premature rupture of the membranes (ICD-10 O42.0, O42.1, O42.2 and O42.9), IHC (O26.6), fear of childbirth (O99.80), diseases of the circulatory system (O99.4) and mental disorders and diseases of the nervous system (O99.3). Pre-eclampsia was defined as a blood pressure of 140/90 or more after 20 weeks of gestation in a woman with previous normal blood pressures. One of the following was additionally required: proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema or cerebral/visual symptoms. GDM was defined as a pathological 2-hour, 75 g oral glucose tolerance test. Placental pathologies included placenta praevia, placental abruption and manual removal of the placenta. IHC is a pregnancy-specific liver disease characterized by raised serum bile acids and maternal itching of the hands and feet. IHC is proposed to be associated with an increased risk for fetal distress and stillbirth, which is why an induction of labor or elective CS is usually recommended at the latest when the pregnancy is full term (Geenes et al. 2014).

4.3.4 STUDY IV

To identify adverse obstetric outcomes in cancer survivors and their siblings, the two cohorts were linked to the MBR. Information on mode of delivery (spontaneous vaginal delivery, instrumental vaginal delivery and overall CS), induction of labor and medical pain relief was available from 1987 onwards. In 1991 CS were further sub-classified into elective (planned) cesarean delivery and urgent cesarean delivery (when there is or might be a threat to the fetus or the mother and the time between the decision to operate and the birth of the fetus should not exceed 30 minutes). From 2004 onwards emergency CS (where the time between decision to operate and the birth of the fetus should not exceed 10 minutes) was also included. Information on prolonged labor (ICD-10 O63.0), anal sphincter injury (ICD-10 O70.2, O70.3 and O70.4) and postpartum hemorrhage was available from 2004 onwards. Asphyxia of the fetus was analyzed from 1991 onwards and defined as pathological changes in the heart rate of the fetus (based on cardiotocography), a scalp blood-pH below 7.05 during delivery or use of ICD-10 code O68 (labor and delivery complicated by abnormality of fetal acid-base balance) or P20 (intrauterine hypoxia). Most outcomes, except prolonged labor and anal sphincter injury, were based on dichotomous variables in the MBR. Induction of labor was performed either by intravaginal or oral administration of misoprostol, dilatation of the cervix by a balloon catheter, intravenous administration of oxytocin or mechanical rupture of the

amniotic membranes. Postpartum hemorrhage was defined as more than a 1,000 ml blood loss during the first 24 hours after delivery.

4.4 STATISTICAL ANALYSES

In Study I, we calculated incidence rate ratio (IRR), whereas in Studies II, III and IV, we calculated odds ratios (ORs) with 95% confidence intervals (CI) for dichotomous outcomes. In rare events (incidence being less than 10%), as is mostly the case in outcomes studied in this thesis, ORs provide a reasonable approximation of the risk (Davies et al. 1998), which is why the term increased/decreased risk is used for statistically significant ORs. It is notable, however, that ORs present associations of increased/decreased risks rather than confirmed causality between exposure and outcome. Level of statistical significance was set at $p < 0.05$ in all the primary analyses.

4.4.1 STUDY I

Study I reports incidence rates of fertility treatments (the number of events per 10,000 person years) and conditional probability of fertility treatment by time period and age of the women. We used the Poisson regression model to calculate IRRs of fertility treatments in cancer survivors and siblings, adjusting for age and calendar time at possible drug purchase. We calculated an overall IRR, assuming no heterogeneity by age and calendar time period. In additional analyses, we report relative excess risks for fertility treatments, compared to a baseline IRR (age 20-24, time period 1993-1997), allowing heterogeneity. We used a likelihood ratio test to calculate the statistical significance of the heterogeneity. Using generalized additive models (Wood et al. 2006), we plotted smoothed incidence rates of any fertility treatments by age and time period of fertility drug purchase. All analyses were carried out using R version 3.5.1.

4.4.2 STUDIES II AND IV

Studies II and IV used univariate and multivariate unconditional logistic regression models to estimate ORs with 95% CIs for dichotomous outcomes, comparing survivors to siblings. We did not perform direct matching of cancer survivors to their siblings (allowing conditional logistic regression models), as it would have diminished the sample to 12% of the entire data available. We performed multivariate subanalyses stratifying by age at cancer diagnosis, cancer treatment, elapsed time

from diagnosis to delivery and cancer type in order to study possible patient-related risk factors. These analyses used Bonferroni correction to take multiple comparisons into account. We analyzed differences in categorical variables between survivors and siblings by using the χ^2-test. Statistical analyses in these two studies were computed by using STATA version 12.1 (StataCorp, College Station, TX).

Study II included multiple pregnancies of the same mother. We used random effects modeling to account for this. In the final analyses, we adjusted for maternal age at delivery, time period of delivery, smoking and parity. In study IV we considered potential confounders to be maternal age at delivery, time period of delivery, gestational age, birth weight, maternal smoking, socioeconomic status, malpresentation and placental pathologies. To identify variables to be included in the final model, a likelihood ratio test was used. In the final analyses, we adjusted for maternal age at delivery, time period of delivery, gestational age and smoking.

4.4.3 STUDY III

Study III sampled five age-matched comparison subjects for every cancer survivor. We performed direct matching, allowing us to use conditional logistic regression models to estimate ORs and 95% CIs for outcomes categorized as dichotomous variables. In the final model, we adjusted for maternal age at delivery, gestational age and maternal smoking. We compared pregnancy-related conditions in preterm (less than 37 gestational weeks) and term pregnancies (37-41 gestational weeks), adjusting for early onset cancer (in addition to maternal age at delivery and maternal smoking) to find explanations for the increased risk of preterm deliveries in cancer survivors. To study whether survivors with a certain pregnancy related outcome had an excess risk of preterm delivery compared to corresponding comparison subjects, we included interactions and tested their significance using likelihood ratio tests.

As in Studies II and IV, we performed subanalyses, stratifying by age at cancer diagnosis, cancer treatment, elapsed time from diagnosis to delivery and cancer type. In this study also, 95% CIs were corrected for multiple comparison with the Bonferroni correction. We analyzed differences between survivors and comparison subjects in categorical variables using the χ^2-test and computed statistical analyses with STATA 14.0.

4.5 ETHICS

The study protocol for Study II, III and IV, including the use of administrative health data, was approved by the National Institute for Health and Welfare (Dnr THL/1/5.05.00/2014) and included an evaluation from the ethical committee. In addition, Study I was also approved by the SII (Dnr KELA/69/522/2014). The research group has acted according to the data protection principles and ethics rules.

5 RESULTS

5.1 FERTILITY TREATMENTS (STUDIES I AND II)

The overall use of fertility drugs between 1993 and 2012 was increased in cancer survivors compared to siblings (Study I). Altogether, 6.1% of female cancer survivors and 3.8% of female siblings used fertility drugs (IRR 1.43, 95% CI 1.25-1.65). In Study II the overall use of fertility treatments between 1991 and 2013 (unpublished results) was in line with the results in Study I (OR 1.48, 95% CI 1.00-2.17) as 3.7% of female cancer survivors giving birth used fertility treatments compared to 1.9% of the female siblings. As for survivors and siblings giving birth between 2004 and 2013, 5.2% of survivors and 2.8% of siblings used fertility treatments (OR 1.84, 95% CI 1.18-2.86). It is notable that we calculated IRRs in Study I, whereas we calculated ORs in Study II (Table 7).

Table 7 Adjusted incidence rate ratios and odds ratios for different fertility treatments between 1993 and 2012 (Study I) and between 1991 and 2013 (Study II, unpublished results) among women with a history of cancer compared to female siblings.

Study I Use of fertility drugs in cancer survivors			
Outcome 1993-2012	Survivors N=8,929 N (%)	Siblings N=9,495 N (%)	Adjusted IRR[1] (95%CI)
Fertility treatment	541 (6.06)	358 (3.77)	**1.43 (1.25-1.65)**
Ovulation induction	189 (2.12)	219 (2.31)	0.83 (0.68-1.02)
ART	348 (3.90)	141 (1.48)	**2.41 (1.97-2.96)**
Study II Fertility treatments among cancer survivors giving birth			
Outcome 1991-2013	Deliveries of survivors N=4,282 N (%)	Deliveries of siblings N=16,787 N (%)	Adjusted OR[2] (95%CI)
Fertility treatment	157 (3.67)	313 (1.86)	**1.48 (1.00-2.17)**
Other fertility treatments	84 (1.96)	174 (1.04)	1.49 (0.96-2.29)
ART	116 (2.71)	250 (1.49)	1.28 (0.83-1.96)

IRR, incidence rate ratio; OR, odds ratio; CI, confidence interval; ART, assisted reproductive technology

[1] Adjusted for age of the woman and year of fertility drug purchase

[2] Adjusted for maternal age, year of delivery, parity and maternal smoking

Statistically significant odds ratios are presented in bold font ($p<0.05$)

5.1.1 USE OF FERTILITY DRUGS IN CANCER SURVIVORS (STUDY I)

Table 8 reports use of fertility drugs according to cancer type in Study I. Cancer types with the highest use of fertility drugs were breast cancer (15.8%), unspecified cancers (8.6%), retinoblastomas (6.5%), lymphomas (6.4%) and thyroid cancer (5.4%).

Table 8 Use of fertility drugs according to cancer type (Study I)

Cancer type				
	Survivors (N=8,929) N (%)	**Any fertility treatment N (%)**	**OI N (%)**	**ART N (%)**
Leukemia	688 (7.71)	22 (3.20) [1]	12 (1.74)	9 (1.31)
Lymphoma	1161 (13.00)	74 (6.37) [1]	24 (2.07)	49 (4.22)
Central Nervous System	970 (10.86)	30 (3.09)	17 (1.75)	13 (1.34)
Sympathetic Nervous System	77 (0.86)	1 (1.30)	1 (1.30)	0 (0.00)
Retinoblastoma	31 (0.35)	2 (6.45)	1 (3.23)	1 (3.23)
Renal Tumors	154 (1.72)	5 (3.25)	3 (1.95)	2 (1.30)
Malignant bone Tumors	140 (1.57)	7 (5.00)	5 (3.57)	2 (1.43)
Soft Tissue and other Sarcomas	338 (3.79)	13 (3.85)	7 (2.07)	6 (1.78)
Germ cell, Gonadal and Trophoblastic neoplasms	523 (5.86)	14 (2.68)	8 (1.53)	6 (1.15)
Carcinomas and other malignant epithelial neoplasms	4517 (50.59)	355 (7.86) [1]	101 (2.24)	253 (5.60)
Digestive system	532 (5.96)	23 (4.32)	16 (3.01)	7 (1.32)
Breast	1402 (15.70)	221 (15.76)	24 (1.71)	196 (13.98)
Melanoma of the skin	705 (7.90)	33 (4.68)	19 (2.70)	14 (1.99)
Thyroid gland	982 (11.00)	53 (5.40)	27 (2.75)	26 (2.65)
Others	896 (10.03)	25 (2.79)	15 (1.67)	10 (1.11)
Unspecified	93 (1.04)	8 (8.60)	5 (5.38)	3 (3.23)
Missing	215 (2.41)	10 (4.65) [1]	5 (2.33)	4 (1.86)

OI, Ovulation induction; ART, assisted reproduction technology

[1] Four survivors were censored after being categorized into the any treatment group, but before categorization into OI or ART treatment group.

Cancer survivors had an increased use of overall fertility treatments and ART compared to siblings (Study I, Table 9). Allowing heterogeneity in IRR between age-groups and time period, the IRR in any fertility treatments and ART was higher from 2003 onwards. For example, IRR for use of ART in survivors compared to siblings was 3.4-fold (95% CI 1.79-6.41) in 2003-2007 compared to that in 1993-1997. Regarding the effect of age at possible fertility drug purchase, a smaller IRR for use of ART among survivors older than 30 years was found compared to survivors aged 20-24 years (Table 9).

Table 9 Adjusted overall incidence rate ratios (IRRs) for different fertility treatments between 1993 and 2012 among female cancer survivors compared to their siblings.

		Any treatment	**OI**	**ART**
Assuming no heterogeneity in IRR by age and time period				
Overall IRR[1]		**1.43 (1.25-1.65)**	0.83 (0.68-1.02)	**2.41 (1.97-2.96)**
Allowing heterogeneity in IRR by age and time period				
Baseline IRR[1] (age 20-24, period 1993-1997)		1.32 (0.75-2.30)	0.60 (0.25-1.42)	2.28 (0.92-5.68)
Relative excess risk compared to baseline IRR				
Age	16-19	-	-	-
	20-24	1	1	1
	25-29	0.66 (0.38-1.16)	1.69 (0.67-4.28)	0.62 (0.25-1.56)
	30-34	0.86 (0.48-1.54)	1.64 (0.67-4.04)	**0.41 (0.17-0.97)**
	35-41	0.59 (0.34-1.02)	1.14 (0.46-2.83)	**0.35 (0.15-0.82)**
Test for heterogeneity		p-value < 0.001	p-value = 0.474	p-value < 0.001
Period	1993-1997	1	1	1
	1998-2002	1.24 (0.81-1.89)	0.91 (0.52-1.59)	1.73 (0.88-3.39)
	2003-2007	**2.31 (1.53-3.49)**	1.01 (0.55-1.87)	**3.39 (1.79-6.41)**
	2008-2012	**1.73 (1.18-2.53)**	0.89 (0.53-1.50)	**2.65 (1.44-4.89)**
Test for heterogeneity		p-value <0.001	p-value = 0.959	p-value < 0.001

IRR, incidence rate ratio; CI, confidence interval; OI, Ovulation induction; ART, Assisted reproductive technology

[1]Adjusted for calendar period and attained age

Statistically significant incidence rate ratios are presented in bold font (p<0.05)

Figure 8 plots incidence rates/10,000 person years for overall fertility treatments against age at fertility drug purchase in four different time periods. Table 10 presents incidence rates for fertility treatments, which were quite similar in cancer survivors and siblings in 1993-1997. In 1998-2002, higher incidence rates for fertility treatments in survivors than in siblings were observed below the age of 30 years. In 2003-2007, the difference in incidence rates for fertility treatments became statistically significant and was at its highest. The biggest difference in incidence rates was seen among women younger than 25 years of age (62/10,000 person years in survivors compared to 15/10,000 person years in siblings). The gap between the incidence rates decreased in 2008-2012, being still higher among survivors compared to siblings in all age groups. The highest difference was among women younger than 25 years of age (51/10,000 person years in survivors compared to 17/10,000 person years in siblings). Regarding incidence rates for ART in survivors and siblings, the results were similar to that of overall fertility treatments. The original publication (Study I) presents detailed information and figures on incidence rates in ART and OI.

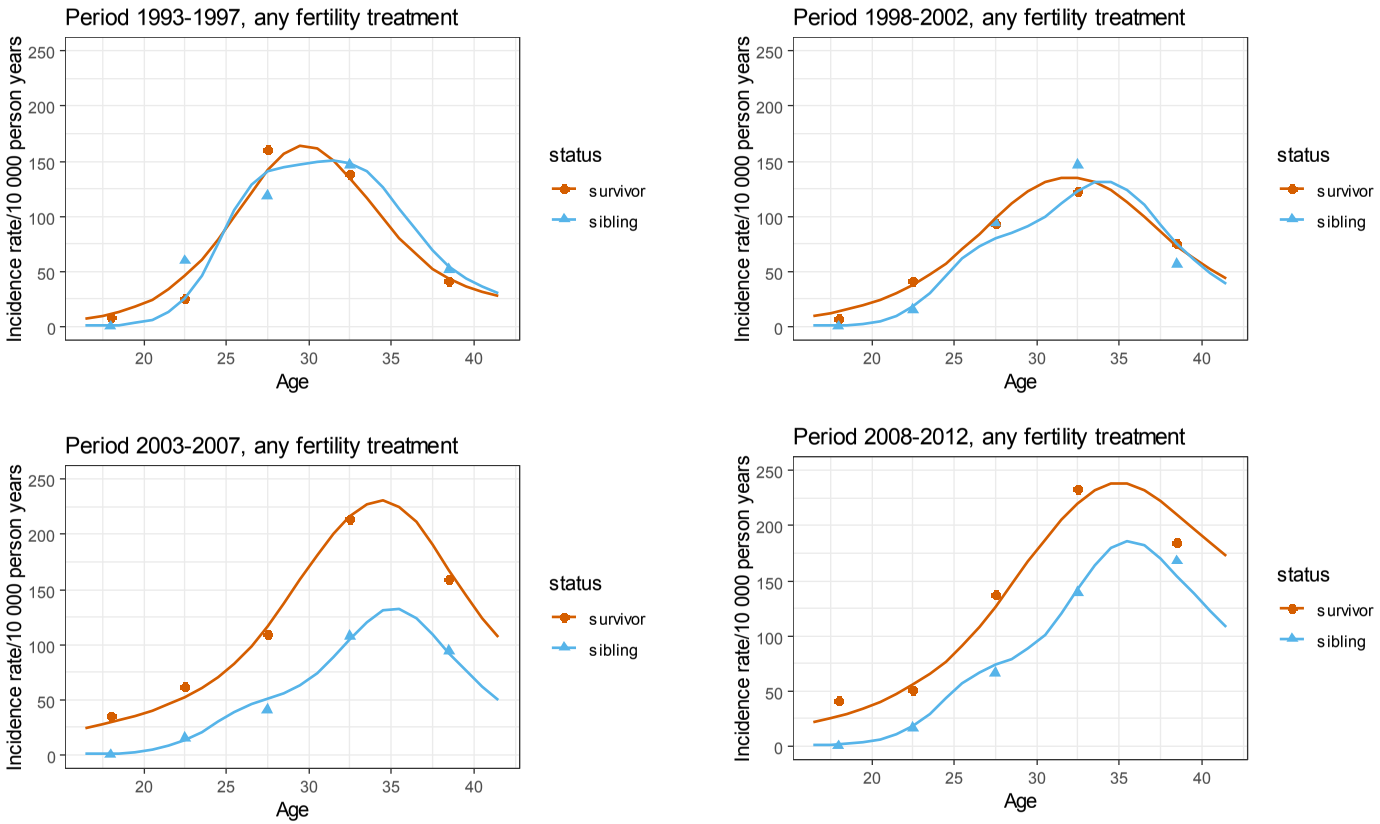

Figure 8 Incidence rates for overall fertility treatments in cancer survivors and siblings according to age at drug purchase in different time periods

Table 10 Incidence rates and conditional probability of any fertility treatments in cancer survivors and siblings by age and time period

		Any fertility treatments (N)		Person years		Incidence rate/10,000 person years		Conditional probability %	
Age	**Period**	**Survivors**	**Siblings**	**Survivors**	**Siblings**	**Survivors**	**Siblings**	**Survivors**	**Siblings**
16-19	1993-1997	1	0	1233	1607	8	0	0.3	0
	1998-2002	1	0	1382	2160	7	0	0.3	0
	2003-2007	5	0	1411	2336	35	0	1.4	0
	2008-2012	6	0	1477	2792	41	0	1.6	0
	Total	**13**	**0**	**5503**	**8895**				
20-24	1993-1997	4	11	1570	1845	25	60	1.3	2.9
	1998-2002	9	4	2174	2650	41	15	2	0.8
	2003-2007	14	5	2273	3268	62	15	3	0.8
	2008-2012	12	6	2354	3624	51	17	2.5	0.8
	Total	**39**	**26**	**8371**	**11387**				
25-29	1993-1997	26	25	1617	2115	161	118	7.7	5.7
	1998-2002	18	18	1931	1906	93	94	4.6	4.6
	2003-2007	27	11	2462	2689	110	41	5.3	2
	2008-2012	36	22	2629	3306	137	67	6.6	3.3
	Total	**107**	**76**	**8639**	**10016**				
30-34	1993-1997	26	40	1872	2724	139	147	6.7	7.1
	1998-2002	22	29	1801	1977	122	147	5.9	7.1
	2003-2007	44	18	2060	1674	214	108	10.1	5.2
	2008-2012	57	32	2437	2303	234	139	11	6.7
	Total	**149**	**119**	**8170**	**8678**				
35-41	1993-1997	28	39	6913	7608	41	51	2.8	3.5
	1998-2002	32	26	4240	4619	75	56	5.1	3.9
	2003-2007	56	27	3532	2863	159	94	10.5	6.4
	2008-2012	60	34	3242	2025	185	168	12.2	11.1
		176	**126**	**17927**	**17115**				

5.1.2 FERTILITY TREATMENTS IN CANCER SURVIVORS GIVING BIRTH (STUDY II)

Study II shows that the survivors giving birth were older than siblings (mean age 31.5 years and 30.1 years, respectively) (p-value<0.001), and survivors were more likely to be primiparous (p-value<0.001). Regarding the age at cancer diagnosis and its association with fertility treatments in cancer survivors giving birth between 1991 and 2013, we found a non-significant tendency for more advanced fertility treatments among cancer survivors treated as young adults (25-34 years of age) compared to siblings (unpublished results, Table 11). Similar results were observed among cancer survivors giving birth between 2004 and 2013, where survivors, treated as young adults, had an increased use of fertility treatments (OR 2.31, 95% CI 1.01-5.32) and ART (OR 3.13, 95% CI 1.03-9.52) compared to siblings. On the contrary, childhood cancer survivors, giving birth in 2004-2013, had the lowest risk for fertility treatments (OR 1.56, 95% CI 0.68-3.61) but an increased risk for IUI (OR 3.42, 95% CI 1.08-10.82) compared to siblings. Note that some women (Table 11) underwent several different fertility treatments before becoming pregnant, which is why the numbers in the different treatment categories do not add up to the numbers in the overall fertility treatment-group.

Table 11 Adjusted odds ratios for fertility treatments between 1991 and 2013 among survivors in respective diagnostic age group, compared with siblings (unpublished results).

Outcome[1]	**Age at diagnosis**							
	Deliveries of siblings (N=16,787)		**0-14 years (N=899)**		**15-24 years (N=1,614)**		**25-34 years (N=1,763)** [2]	
	n (%)	**OR (95%CI)**	**n (%)**	**OR (95%CI)**	**n (%)**	**OR (95%CI)**	**n (%)**	**OR (95%CI)**
Fertility treatment	313 (1.86)	1	25 (2.78)	1.41 (0.63-3.15)	52 (3.22)	1.60 (0.90-2.83)	80 (4.54)	1.49 (0.85-2.60)
Other fertility treatment	250 (1.49)	1	15 (1.67)	1.74 (0.70-4.35)	30 (1.86)	1.78 (0.95-3.37)	39 (2.21)	1.23 (0.64-2.34)
ART	174 (1.04)	1	16 (1.78)	1.13 (0.44-2.90)	35 (2.17)	1.25 (0.65-2.39)	65 (3.69)	1.41 (0.78-2.54)

OR, odds ratio; CI, confidence interval
[1]Adjusted for maternal age, year of delivery, parity and maternal smoking
[2]Only siblings giving birth at the age of 25 years or older included

Time elapsed between cancer diagnosis and delivery played a central role among cancer survivors giving birth between 1991 and 2013 (unpublished results). We observed that the odds for fertility treatments increased over time, being lowest less than six years from treatment and highest 11-34 years from cancer treatments concerning both ART and other fertility treatments (Table 12). Similar results were observed among cancer survivors giving birth between 2004 and 2013.

Table 12 Adjusted odds ratios for fertility treatments between 1991 and 2013 among survivors according to time between cancer diagnosis and delivery, compared to siblings (unpublished results).

Outcome[1]	**Elapsed time from cancer treatment to delivery**							
	Deliveries of siblings (N=16,787)		**Less than 6 years (N=1,307)**		**6-10 years (N=1,319)**		**11-34 years (N=1,656)**	
	n (%)	**OR (95%CI)**	**n (%)**	**OR (95%CI)**	**n (%)**	**OR (95%CI)**	**n (%)**	**OR (95%CI)**
Fertility treatment	313 (1.86)	1	32 (2.45)	1.01 (0.50-2.02)	48 (3.64)	1.38 (0.78-2.44)	77 (4.65)	**2.00 (1.09-3.68)**
Other fertility treatments	174 (1.04)	1	17 (1.30)	1.02 (0.45-2.31)	27 (2.05)	1.46 (0.74-2.87)	40 (2.42)	1.88 (0.94-3.75)
ART	250 (1.49)	1	27 (2.07)	1.09 (0.52-2.25)	34 (2.58)	1.12 (0.59-2.13)	55 (3.32)	1.69 (0.96-2.97)

OR, odds ratio; CI, confidence interval
[1]Adjusted for maternal age, year of delivery, parity and maternal smoking
Statistically significant odds ratios are presented in bold font

Sub-analyses on fertility treatments leading to birth according to different cancer types, mostly resulted in such small numbers that reporting them was not sensible. Notable, however, was the increased use of fertility treatments in thyroid cancer survivors compared to siblings (OR 2.72, 95% CI 1.26-5.86), as 39 (5.4%) of all thyroid cancer survivors giving birth in 1991-2013 had undergone fertility treatments (unpublished results).

5.2 PREGNANCY-RELATED CONDITIONS (STUDY III)

This study, placed focus on pregnancy-related conditions, exploring possible conditions that could explain the increased risk of preterm delivery previously observed in cancer survivors (Signorello et al. 2006, Madanat-Harjuoja et al. 2010, van der Kooi et al. 2018). In addition to the original results, it presents new unpublished data on placental pathologies, malpresentation, diseases of the circulatory system and use of LMWH medication in cancer survivors compared to comparison subjects. Preterm deliveries were more common among cancer survivors compared to comparison subjects, as 7.4% of cancer survivors and 5.2% of comparison subjects delivered preterm (less than 37 gestational weeks) (p=0.004). Regarding different time periods of delivery, the prevalence of preterm delivery was similar in 1991-2003 and 2004-2013. Table 13 shows that cancer survivors delivered at a higher age than the population comparisons (mean age 29.7 and 27.6 years, respectively, p<0.001) and more often during the most recent time period (2003-2013, p<0.001).

Pregnancy-related conditions were divided into those possibly resulting in spontaneous preterm delivery and those possibly leading to medically induced preterm delivery. We did not observe an increased risk (Table 14) for conditions possibly leading to spontaneous preterm delivery (threatened preterm labor and preterm rupture of the membrane). However, with regard to maternal pregnancy-related conditions possibly leading to medically induced preterm delivery, cancer survivors had an increased risk for IHC, fear of childbirth, mental disorders and diseases of the nervous system, as well as use of LMWH medication (Table 14). The overall risk was not increased for pre-eclampsia, vaginal bleeding, placental pathologies, GDM, malpresentation or diseases of the circulatory system. However, we observed an increased risk for overall hospitalization. A separate analysis according to year of delivery revealed that the risk for overall hospitalization in cancer survivors compared to comparison subjects was lower during the most recent time period of 2003-2013 (OR 1.30, 95% CI 1.02-1.65) than 1991-2002 (OR 1.55, 95% CI 1.22-1.97).

To study whether cancer survivors with a certain pregnancy related outcome had an excess risk of preterm delivery compared to corresponding comparison subjects and survivors without the pregnancy-related condition, we performed a separate analysis. We observed an increased risk for preterm delivery in survivors with vaginal bleeding (OR 1.35, 95% CI 1.07-247 1.71) and pre-eclampsia (1.35, 95% CI 1.06-1.72) compared to comparison subjects with the same condition. The original publication (Study III) describes these results in detail.

Table 13 Diagnostic characteristics of female cancer survivors and descriptive characteristics of post-diagnosis first pregnancies of survivors and a comparison group.

Characteristics	Subcategory	Survivors (N=1,753) N (%)	Comparisons (N=5,123) N (%)	P-value
Year of diagnosis	1957-1972	12 (0.68)	-	
	1973-1992	666 (37.99)	-	
	1993-2012	1,075 (61.32)	-	
Age at diagnosis	0-14	398 (22.70)	-	
	15-24	770 (43.92)	-	
	25-39	585 (33.37)	-	
Time from diagnosis to delivery (years)	0-5	729 (41.59)	-	
	6-10	474 (27.04)	-	
	11-38	550 (31.37)	-	
Cancer treatment	Chemotherapy	556 (31.72)	-	
	Radiotherapy	559 (31.89)	-	
	Surgery, only	712 (40.62)	-	
	Missing	219 (12.49)	-	
Age at delivery	<25	331 (18.88)	1,515 (29.57)	**<0.001**
	25-29	599 (34.17)	2,111 (41.21)	
	30-34	552 (31.49)	1,149 (22.43)	
	35 or more	271 (15.46)	348 (6.79)	
Time period of delivery	1991-2002	665 (37.93)	2,585 (50.46)	**<0.001**
	2003-2013	1,088 (62.07)	2,538 (49.54)	
Maternal smoking	No	1,494 (85.23)	4,130 (80.62)	0.056
	Yes	227 (12.95)	885 (17.28)	
	Missing	32 (1.83)	108 (2.11)	
Gestational age	<32	32 (1.83)	42 (0.82)	**0.004**
	32-36	97 (5.53)	226 (4.41)	
	37-41	1,513 (86.31)	4,528 (88.39)	
	42 or more	109 (6.22)	316 (6.17)	
	Missing	2 (0.11)	11 (0.21)	
Birth weight (g)	<1500	31 (1.77)	36 (0.70)	**0.002**
	1500-2499	73 (4.16)	163 (3.18)	
	2500-3999	1,421 (81.06)	4,218 (82.33)	
	4000-4499	205 (11.69)	619 (12.08)	
	4500 or more	23 (1.31)	87 (1.70)	

Table 14 Adjusted odds ratios (ORs) for pregnancy outcomes between 1991 and 2013 among female cancer survivors with their first post diagnosis pregnancy compared with first pregnancies in a matched female group (unpublished results on placental pathologies, malpresentation, diseases of the circulatory system and use of LMWH medication)

Pregnancy outcome	Survivors N=1,753 (%)	Controls N=5,123 (%)	Adjusted OR[1] (95%CI)
Any hospitalization	394 (22.48)	906 (17.68)	**1.45 (1.25-1.68)**
Pregnancy outcomes possibly leading to spontaneous preterm delivery			
Hospitalization for threatened preterm labor	49 (2.80)	105 (2.05)	1.39 (0.91-2.12)
Preterm rupture of the membranes[2]	41 (4.08)	68 (3.04)	1.21 (0.67-2.17)
Pregnancy outcomes possibly leading to medically induced preterm delivery			
Hospitalization for pre-eclampsia	97 (5.53)	258 (5.04)	1.11 (0.85-1.45)
Hospitalization for vaginal bleeding	24 (1.37)	52 (1.02)	1.31 (0.74-2.31)
Placental pathologies	49 (2.80)	107 (2.09)	1.07 (0.73-1.57)
Gestational diabetes[2]	109 (10.85)	196 (8.77)	1.06 (0.78-1.43)
Intrahepatic cholestasis[2]	18 (1.79)	20 (0.89)	**2.86 (1.09-7.49**)
Malpresentation	151 (8.61)	420 (8.20)	0.98 (0.80-1.21)
Fear of childbirth[2]	42 (4.18)	46 (2.06)	**2.25 (1.31-3.85)**
Mental disorders and diseases of the nervous system[2]	28 (2.79)	16 (0.72)	**5.89 (2.31-15.00)**
Diseases of the circulatory system[2]	4 (0.40)	4 (0.18)	3.65 (0.37-35.83)
Use of LMWH medication[2]	28 (2.79)	22 (0.98)	**2.76 (1.26-6.03)**

OR, odds ratio; CI, confidence interval; LMWH, low molecular weight heparin
[1]Adjusted for maternal age, gestational age and maternal smoking
[2]Data available from 2004-2013 (1,005 survivors and 2,236 female controls)
Statistically significant odds ratios are presented in bold font

As many as 9.3% of childhood cancer survivors, 6.5% of survivors diagnosed as adolescents and 7.2% of survivors diagnosed as young adults delivered preterm. Regarding maternal pregnancy-related conditions, the risks were most elevated in adolescents. This group had the highest risk for overall hospitalization (OR 1.62, 95% CI 1.24-2.10), hospitalization for vaginal bleeding (OR 2.83, 95% CI 1.11-7.18) and fear of childbirth (OR 3.72 95% CI 1.15-12.02) compared to comparison subjects.

Regarding preterm delivery according to elapsed time between cancer diagnosis and delivery, 6.9% of all survivors delivering within six years of cancer diagnosis had a preterm delivery, whereas the number for those delivering 6-11 years after cancer diagnosis was 6.3%; it was 8.9% for those delivering more than 11 years after cancer diagnosis. The risk for overall hospitalization was highest among those delivering less than six years from cancer diagnosis (OR 1.75, 95% CI 1.34-2.30), second highest among those delivering 6-10 years from cancer diagnosis (OR 1.43, 95% CI 1.01-2.03).

The risk for hospitalization did not increase in women delivering 11 years or more after cancer diagnosis (OR 1.08, 95% CI 0.75-1.54).

Among cancer survivors treated with chemotherapy, 9.9% delivered preterm. The prevalence was 7.3% among survivors treated with radiotherapy. A separate analysis of those treated with abdominal radiotherapy (107 survivors) revealed that 7.8% delivered preterm. Of survivors treated with surgery, 6.5% were preterm deliveries. The risk for overall hospitalization showed an increase in all treatment-groups but was highest among survivors treated with surgery (OR 1.58, 95% CI 1.16-2.14). Cancer types with the highest number of preterm deliveries were renal tumors (30.0%), tumors of the sympathetic nervous system (16.7%), leukemia (13.9%) and malignant bone tumors (13.5%). The original publication (Study III) presents a descriptive supplemental table on pregnancy-related conditions according to cancer type.

5.3 OBSTETRIC OUTCOMES (STUDY IV)

Study IV focused on obstetric outcomes in cancer survivors compared to siblings. It also presents new unpublished data on prolonged labor, fetal asphyxia, emergency CS and anal sphincter injury in addition to the original results. In our data, cancer survivors were older compared to siblings ($p<0.001$). Cancer survivors also had more preterm deliveries and lower birth weight of the offspring and delivered more often in the most recent time periods compared to siblings ($p<0.001$). Survivors were less likely to smoke than their siblings ($p<0.001$).

Table 15 shows that cancer survivors had an increased risk for induction of labor (OR 1.17 95% CI 1.02-1.35) and elective CS (OR 1.36 95%CI 1.11-1.67). However, the overall risk for urgent or emergency CS did not increase in cancer survivors. Common indications for urgent or emergency CS are prolonged labor or suspicion of fetal asphyxia, which was not increased in cancer survivors compared to siblings. Table 16 presents different types of medical pain relief during vaginal delivery (unpublished results). We observed a crude, unadjusted increased risk for any medical pain relief as well as epidural and spinal anaesthesia in survivors compared to siblings. However, after adjusting for maternal age, year of delivery, gestational age and maternal smoking, only the use of spinal anaesthesia was increased.

Table 15 Adjusted odds ratios (ORs) for obstetric outcomes among cancer survivors giving birth compared to siblings (unpublished results on prolonged labor, fetal asphyxia, emergency CS and anal sphincter injury).

Obstetric outcome	Survivors N=1,800 (%)	Siblings N=7,137 (%)	Adjusted OR[1] (95%CI)
Induction of labor	344 (19.1)	1,113 (15.6)	**1.17 (1.02-1.35)**
Prolonged labor[3]	67 (8.44)	186 (8.88)	0.88 (0.65-1.19)
Fetal asphyxia[2]	86 (5.28)	252 (4.35)	1.05 (0.81-1.35)
Vaginal birth	1,120 (62.2)	4,960 (69.5)	**0.87 (0.78-0.97)**
Instrumental vaginal birth	241 (13.4)	793 (11.1)	1.07 (0.91-1.25)
Cesarean section	424 (23.6)	1,329 (18.6)	**1.15 (1.01-1.31)**
Elective CS[2]	153 (9.4)	375 (6.5)	**1.36 (1.11-1.67)**
Urgent CS[2]	243 (14.9)	750 (13.00)	1.04 (0.89-1.23)
Emergency CS[3]	21 (2.64)	37 (1.77)	1.47 (0.85-2.54)
Anal sphincter injury[3]	13 (1.64)	29 (1.38)	1.13 (0.58-2.20)
Postpartum hemorrhage[3]	34 (4.3)	72 (3.4)	1.19 (0.78-1.81)

OR, odds ratio; CI, confidence interval
[1]Adjusted for maternal age, year of delivery, gestational age and maternal smoking
[2]Data available from 1991-2013 (1630 survivors, 5790 siblings)
[3]Data available from 2004-2013 (794 survivors, 2,094 siblings)
Statistically significant odds ratios are presented in bold font

Table 16 Crude and adjusted odds ratios (ORs) for medical pain relief among cancer survivors with vaginal delivery compared to siblings (unpublished results).

Obstetric outcome	Survivors N=1,374 (%)	Siblings N=5,800 (%)	Unadjusted OR (95%CI)	Adjusted OR[1] (95%CI)
Any medical pain relieve	1,129 (82.17)	4,499 (77.57)	**1.33 (1.15-1.55)**	0.89 (0.75-1.06)
Epidural analgesia	739 (53.78)	2,803 (48.33)	**1.24 (1.10-1.40)**	0.92 (0.81-1.05)
Spinal anaesthesia[3]	43 (7.20)	83 (4.99)	**1.48 (1.01-2.16)**	**1.51 (1.03-2.22)**
Paracervical block anaesthesia	229 (16.67)	1,028 (17.72)	0.93 (0.79-1.09)	1.02 (0.86-1.19)
Pudendal nerve block	53 (3.86)	200 (3.45)	1.12 (0.83-1.53)	0.83 (0.60-1.13)
Systemic nitrous oxide[2]	757 (61.44)	2,749 (59.00)	1.11 (0.97-1.26)	1.06 (0.93-1.21)
Other medical pain relieve[3]	112 (18.76)	328 (19.74)	0.94 (0.74-1.19)	0.98 (0.77-1.25)

OR, odds ratio; CI, confidence interval
[1]Adjusted for maternal age, year of delivery, gestational age and maternal smoking
[2]Data available from 1991-2013 (1,232 survivors, 4,659 siblings)
[3]Data available from 2004-2013 (597 survivors, 1,662 siblings)
Statistically significant odds ratios are presented in bold font

Sub-analyses according to age at cancer diagnosis revealed that cancer survivors treated in their childhood had the highest risks for adverse obstetric outcomes. They had the highest risk for induction of labor (OR 1.38, 95% CI 1.02-1.86) and overall CS (OR 1.48, 95% CI 1.11-1.96) and this was the only diagnostic age group with an increased risk for urgent CS (OR 1.40 95% CI 1.02-1.94). This group also had the lowest odds for normal vaginal delivery (OR 0.70, 95% CI 0.54-0.90). In contrast, we found no increased risks for those survivors diagnosed with cancer in adolescence or as young adults.

Regarding cancer treatment, survivors treated with chemotherapy had the highest risk for adverse obstetric outcomes as the risk for induction of labor (OR 1.43, 95% CI 1.09-1.87), overall CS (OR 1.42, 95% CI 1.10-1.83) and urgent CS (OR 1.37, 95% CI 1.08-1.75) were increased. Survivors treated with radiotherapy did not have an increased risk for any of the outcomes studied. A separate analysis of 96 survivors treated with abdominal radiotherapy revealed no increased risks compared to siblings, but the numbers were small. Studying obstetrics outcomes according to cancer type revealed that, survivors treated for CNS tumors had an increased risk for overall CS (OR 1.69, 95% CI 1.22-2.33) and elective CS (OR 2.14, 95% CI 1.34-3.42).

Table 17 describes the adjusted ORs for different obstetric outcomes among cancer survivors and siblings who underwent CS. Survivors had a higher proportion of fear of childbirth, pre-eclampsia and inductions of labor than siblings. However, none of the outcomes were significantly increased in survivors compared to siblings.

Table 17 Adjusted odds ratios (ORs) for obstetric outcomes during 1991 to 2013 among cancer survivors and siblings undergoing cesarean sections (unpublished results).

Obstetric outcome	Survivors with CS N=396 (%)	Siblings with CS N=1,125 (%)	Adjusted OR[1] (95%CI)
Fear of childbirth[2]	19 (9.64)	28 (6.48)	1.60 (0.85-3.00
Pre-eclampsia	38 (9.60)	98 (8.71)	1.06 (0.70-1.59)
Gestational diabetes[2]	20 (10.15)	51 (11.81)	0.86 (0.49-1.52)
Malpresentation	107 (27.02)	326 (28.98)	0.90 (0.69-1.17)
Placental pathology	7 (1.77)	26 (2.31)	0.70 (0.30-1.66)
Induction of labor	78 (19.70)	209 (18.58)	1.08 (0.79-1.47)
Long labor[2]	24 (12.18)	77 (17.82)	0.71 (0.42-1.18)
Fetal asphyxia	47 (11.87)	131 (11.64)	0.94 (0.65-1.34)

CS, cesarean section; OR, odds ratio; CI, confidence interval
[1]Adjusted for maternal age, year of delivery, gestational age and maternal smoking
[2]Data available from 2004-2013 (794 survivors, 2,094 siblings)

5.3.1 BIRTH RATES (STUDY IV)

Study IV calculated the birth rates in cancer survivors, according to age at cancer diagnosis in different cancer types (Table 18). The entire cohort comprised 13,799 cancer survivors diagnosed at the age of 0-34 years. Of 2,765 female childhood cancer survivors, 487 (17.6%) delivered at least one child later in life. Of 2,707 cancer survivors, diagnosed as adolescents, 886 (32.7%) delivered at least one child after cancer diagnosis. In our cohort, 8,327 survivors were diagnosed with cancer as young adults. Of these cancer survivors, 1,028 women (12.3%) delivered after their cancer diagnosis at the end of our follow up in December 2013.

Table 18 Numbers and percentages of female cancer survivors with deliveries at least 9 months after cancer diagnosis, by primary site of cancer and age at cancer diagnosis.

	Cancer survivors with deliveries			All female cancer survivors		
Age at diagnosis	**0-14**	**15-24**	**25-34**	**0-14**	**15-24**	**25-34**
Primary site	**n (%)**			**n**		
Leukemia	161 (18.6)	32 (14.5)	9 (3.4)	868	220	263
Lymphoma	46 (21)	212 (39.1)	129 (17.3)	219	542	744
CNS	83 (12.0)	81 (23.5)	70 (9.1)	690	344	771
Symp Nervous Syst	19 (11.4)	3 (17.6)	5 (29.4)	166	17	17
Retinoblastoma	13 (16.0)	0	0	81	0	0
Renal Tumors	36 (20.9)	7 (36.8)	10 (11.2)	172	19	89
Hepatic Tumors	0	0	1 (2.2)	18	15	46
Malignant bone	18 (18.2)	27 (22.1)	7 (6.8)	99	122	103
Soft tissue and other Sarcomas	39 (22.5)	75 (29.6)	67 (13.9)	173	253	481
Germ Cell, Gonadal, Trophobl	10 (12.2)	52 (23.0)	42 (7.7)	82	226	546
Carcinomas and other malign. epith. neopl.	60 (35.9)	389 (42.8)	679 (13.2)	167	908	5160
Thyroid	11 (28.2)	160 (46.0)	242 (24.2)	39	348	999
Cervix	0	3 (10.7)	32 (4.7)	0	28	679
Uterus	0	0	1 (1.4)	0	2	71
Breast	1 (100)	8 (21.1)	110 (6.6)	1	38	1,665
Stomach	0	1 (10.0)	6 (3.4)	0	10	177
Colon	28 (45.9)	78 (47.9)	50 (15.9)	61	163	315
Melanoma	7 (36.8)	98 (51.6)	169 (23.3)	19	190	724
Other Carcinomas	13 (27.7)	36 (27.9)	67 (12.6)	47	129	530
Others	2 (6.7)	8 (19.5)	9 (8.4)	30	41	107
Total	487 (17.6)	886 (32.7)	1,028 (12.3)	2,765	2,707	8,327

6 DISCUSSION

6.1 FERTILITY TREATMENTS

Parenthood is less probable among cancer survivors (Madanat et al. 2008) and they also have lower pregnancy rates compared to the general population (Stensheim et al. 2011, Anderson et al. 2018). With regard to infertility and fertility treatments in cancer survivors, only a few studies exist in the literature, most of them with a follow up that ends in an earlier time period than ours (Barton et al. 2013 and Haggar et al. 2014, Luke et al 2016).

Study I found that cancer survivors had an increased use of fertility drugs compared to female sibling. This is in discordance with the American Childhood Cancer Survivor Study (Barton et al. 2013), in which cancer survivors were less likely (RR 0.57) to be prescribed fertility drugs compared to their siblings, although they had an increased risk (RR 1.48) of clinical infertility (defined as more than one year of unsuccessful attempts at conception) and were as likely as their siblings to seek medical help for their condition.

A sub-classification of fertility treatments into OI and ART showed that the overall increased use of fertility drugs could be explained by the increased use of ART, which was 2.4-fold in cancer survivors compared to siblings. The use of OI was similar in cancer survivors and siblings. OI is usually considered the first line treatment in ovulation disorders and unexplained infertility, as it is non-invasive, less expensive and easier to perform than ART. OI was more common than ART in siblings in our data. However, among cancer survivors, ART was more common, probably because of higher success rates, especially when the ovarian reserve is reduced. It is well known that cancer treatments, especially abdominal radiotherpay and chemotherapy with alkylating agents, may damage the ovaries, leading to a narrowed fertile time window in cancer survivors (Wallace et al. 1989, Anderson et al. 2013, Freour et al. 2017). This probably explained the increased use of more advanced fertility treatments (ART) at the cost of easier, less invasive fertility treatments (OI) in cancer survivors.

Time period played a central role in use of overall fertility treatments and ART, increasing from 2003 onwards in survivors compared to siblings (Study I). Comparing our results to the American childhood cancer survivor study (Barton et al. 2013), it is noteworthy that the results in their study are from an earlier time period, between 1992 and 2004, compared to ours. After this several studies (Meirow et al. 2014,

Oktay et al. 2015 and Goldrat et al. 2015) stated that, although limited data are available, fertility treatments do not seem to increase the risk for cancer recurrence. According to one study on breast cancer patients undergoing ART compared to breast cancer patients without fertility treatments, no differences were found in overall survival rates and relapse of cancer (Goldrat et al. 2015). In the light of these findings, it is possible that the use of fertility treatments has also increased in American cancer survivors during recent years.

Study II analyzed the association of being a cancer survivor giving birth and using fertility treatments. The use of overall fertility treatments in cancer survivors giving birth from 1991-2013 was increased in survivors compared to siblings. An even higher use of fertility treatments was observed among survivors giving birth from 2004-2013. However, a sub-classification of overall fertility treatments into OI, IUI and ART revealed no increased risks in cancer survivors compared to siblings. We found one study (Haggar et al. 2014) similar to ours that analyzed the risk of fertility treatments in cancer survivors giving birth. They found an increased use of fertility treatments in cancer survivors compared to a control group without cancer (RR 1.94). However, that study did not take into account different cancer treatments, age at cancer diagnosis or elapsed time between cancer treatment and delivery. Survivors included in that study were 15-39 years of age at cancer diagnosis, and the follow up ended in 2007.

Our two studies on fertility treatments in cancer survivors and their siblings, showed similar results. Differences in the two studies included the study design (Study I calculated IRR and Study II ORs) and cohort size of the cancer survivors which was more than two-fold in Study I compared to Study II. Study I analyzed the use of fertility treatments between 1993 and 2012 and included only women without biological children. Study II analyzed fertility treatments between 1991 and 2013 and included subsequent pregnancies of the same mother.

6.2 PREGNANCY-RELATED CONDITIONS

Study III assessed pregnancy-related outcomes in cancer survivors and age-matched female comparisons. Our aim was to identify the underlying reasons for the increased risk of preterm deliveries in cancer survivors, observed in several previous studies (Madanat-Harjuoja et al. 2010, Anderson et al. 2017 and van der Kooi et al. 2018). This was done by dividing pregnancy-related conditions in cancer survivors and comparison subjects into those leading to spontaneous preterm delivery and those leading to medically induced preterm delivery.

Studies have shown that especially abdominal irradiation and chemotherapy with busulfan can damage the uterus (Larsen et al. 2004, Beneventi et al. 2015), resulting in fibrosis and reduced blood flow. This, in turn, could lead to premature contractions and rupture of the amniotic membranes, possibly resulting in spontaneous preterm delivery. In our study, being a cancer survivor was not associated with an increased risk for conditions leading to spontaneous preterm delivery (premature rupture of the amniotic membranes or hospitalization for threatened preterm labor) compared to matched comparison subjects. Cancer survivors with hospitalization for threatened preterm labor or premature rupture of amniotic membranes did not have a higher risk than that of corresponding comparison subjects for preterm delivery either. Only a few studies (Green et al. 2010, Haggar et al. 2014, Reulen et al. 2017) exist that investigated pregnancy-related outcomes possibly leading to spontaneous preterm delivery and similar to our study, they found no increased risk in cancer survivors compared to siblings or healthy female controls. One explanation for the similar risk of spontaneous preterm delivery in survivors and comparison subjects could be that cancer survivors with a severely damaged uterus due to toxic cancer treatments could not achieve pregnancy in the first place. A Danish study (Winther et al. 2008) found cancer survivors treated with abdominal radiotherapy to have an increased risk for spontaneous abortion, possibly indicating that radiation-induced damage in the uterus might complicate the implantation of the embryo and lead to early pregnancy loss.

Concerning pregnancy-related conditions possibly leading to medically induced preterm delivery, being a cancer survivor was associated with an increased risk for fear of childbirth, IHC, mental disorders and diseases of the nervous system, use of LMWH medication and overall hospitalization during pregnancy compared to comparison subjects. When comparing our results to other studies on pregnancy outcomes possibly leading to medically induced preterm delivery, we found that the results were conflicting. Previous studies (Green et al. 2010, Haggar et al. 2014, Reulen et al. 2017) found an increased risk for pre-eclampsia and GDM in cancer survivors, especially among those treated with abdominal irradiation, whereas we observed no overall increased risk for these outcomes. Regarding pre-eclampsia, it is notable that our study measured cases of pre-eclampsia requiring hospitalization, leaving out the less severe pre-eclampsia cases, possibly affecting the result. In additional analyses of the reasons behind the preterm deliveries in cancer survivors, we observed that both vaginal bleeding and pre-eclampsia in cancer survivors were associated with an increased risk for preterm delivery compared to corresponding comparison subjects. Our findings may indicate that these conditions are more severe among cancer survivors, as they more often lead to preterm delivery in

survivors compared to comparison subjects with the same condition. However, the policy to induce labor or perform CS varies among physicians, and awareness of a previous cancer may have affected their decision to terminate the pregnancy. This could also explain the higher risk of hospitalization among cancer survivors during pregnancy.

We have found no previous reports on fear of childbirth, mental disorders and diseases of the nervous system, IHC or use of LMWH medication during pregnancy in cancer survivors. According to two studies (Saisto et al. 1999, Melender et al. 2002), 6-10% of pregnant women in the Nordic countries suffer from fear of childbirth. Fear of childbirth is often the underlying reason for a mothers request for CS (Nieminen et al. 2017). It also goes hand in hand with mental disorders, as women with fear of childbirth are twice as likely to suffer from mental health problems compared to women without fear of childbirth (Rouhe et al. 2011). The most common mental disease in pregnant women is depression with a prevalence of 10-15% among all pregnant women (Gavin et al. 2005). In an American study, cancer survivors reported medication use for anxiety and depression at rates nearly two times those reported by the general population (Hawkins et al. 2017). Other studies have reported an increased risk for psychological distress and psychosocial problems, especially in survivors diagnosed as AYAs (Mody et al. 2008, Krull et al. 2010). If left unaddressed and untreated, anxiety and depression in cancer survivors have been found to affect negatively on health behavior (Stark et al. 2002), which could lead to mental disorders and fear of childbirth emerging during pregnancy.

One Scandinavian study (Asdahl et al. 2016) on childhood cancer survivors showed that cancer survivors have an overall increased risk for liver diseases (RR 1.60). In the light of these findings, it is not surprising that being a cancer survivor was associated with an increased risk for IHC compared to comparison subjects in our study. Being a cancer survivor was also associated with an increased use of LMWH medication during pregnancy compared to comparison subjects. This is a new, but not surprising, finding. According to one study by Bajzar et al., childhood cancer patients have a prevalence of 7-14% for symptomatic DVT and a more than 40% prevalence of an asymptomatic DVT (Bajzar et al 2006). Concerning cancer treatments, chemotherapy was most often associated with a DVT in childhood cancer patients (Mitchell et al. 2010). Antithrombotic therapy with LMWH is recommended for pregnant women with a history of DVT (Bates et al. 2018), presumably explaining the increased use of LMWH medication among cancer survivors in our study. Scheduled delivery with prior discontinuation of LMWH is suggested (Bates et al. 2018), potentially increasing the risk for induction of labor in these women. In addition, women with

hospitalization due to threatened preterm labor are often treated with LMWH (Duhl et al. 2007).

In order to identify cancer survivors with cardiac diseases, due to cardiotoxic cancer treatments, we studied the risk for diseases of the circulatory system complicating pregnancy, childbirth or puerperium (ICD-10 code O99.4) in cancer survivors. Being a cancer survivor was not associated with an increased risk for diseases in the circulatory system during pregnancy compared to comparison subjects in our data, but the numbers were small (4 survivors and 4 comparison controls). In a previous study (Hines et al. 2016), the prevalence for pregnancy-associated cardiomyopathy in cancer survivors was 0.3%; surveillance for cardiomyopathy before pregnancy or during the first trimester of pregnancy is recommended in survivors treated with anthracyclins or chest irradiation (Armenian et al. 2015).

Our study found that the proportion of preterm deliveries in cancer survivors during the time period of 1991-2002 and 2003-2013 was similar (7.4%). The total rate of preterm deliveries in Finnish women is low compared to the rest of Europe (Räisänen et al. 2013) and has remained stable during the current decade, being 5.3% in 2017 (Statistics Finland 2018).

6.3 OBSTETRIC OUTCOMES

When we conducted our study on obstetric outcomes in cancer survivors and their siblings, only a few previous studies (Clark et al. 2007, Muller et al. 2009, Haggar et al. 2014) were available on these outcomes. Similar to ours, they found an overall increased risk for CS in cancer survivors. Our study subclassified overall CS into elective, urgent and emergency CS. Only the risk for elective CS was increased. This was a new finding then, which has later been verified in two other studies (Reulen et al. 2017, van der Kooi 2018), that found an increased risk (RR 1.39 and 1.59, respectively) for cancer survivors to opt for elective CS compared to the general population.

It is reassuring that the increased risk for overall CS is explained by elective CS (where the decision to operate is made before onset of delivery), as urgent and emergency CS are associated with higher risks for complications (Krebs et al. 2003, Pallasmaa et al. 2010). According to a Finnish study (Pallasmaa et al. 2010), there was a two-fold increased risk for intraoperative complications and infections in urgent CS compared to elective CS. Our further analyses comparing cancer survivors with CS to siblings with CS revealed no significant differences in cancer survivors and siblings.

However, we observed higher rates of fear of childbirth, pre-eclampsia and induction of labor in cancer survivors delivering by CS compared to corresponding siblings.

Being a cancer survivor was associated with an increased risk for induction of labor when compared to siblings. We found only one previous study on induction of labor (Clark et al. 2007), which reported no increased risk. In that study the follow up ended in 2004, and the difference in CS rates in cancer survivors and controls was quite big (27.3% and 17.2%, respectively), whereas the difference in induction rates was quite small (29.6% and 27.8%, respectively). It is possible that the pregnancies in these cancer survivors were rather terminated by CS than induction of labor.The rates of induction of labor are increasing worldwide, being 20-30% in the Western world (Zeitlin et al. 2013). In 2013, 20.5% of all deliveries in Finland were induced compared to 28.9% in 2017 (Statistics Finland 2018). One Finnish study found that induction of labor was associated with an increased risk for CS by up to 37% (Kruit et al. 2015). However, there are conflicting results, and two other studies (Rattigan et al. 2013 and Little et al. 2017) found that elective induction of labor did not increase the risk for CS and even reduced the risk for neonatal morbidity and possible stillbirth (Little et al. 2017). Our study found that the increased risk for induction of labor did not explain the increased risk for CS in cancer survivors.

The association between being a cancer survivor and the increased risk for induction of labor and elective CS may be partially explained by the increased OR for fear of childbirth, mental disorders and diseases of the nervous system, IHC and use of LMWH medication during pregnancy. These are all conditions known to increase the risk for induction of labor and CS (Nieminen et al. 2017, Tanne et al. 2008, Geenes et al. 2014 and Bates et al. 2018). However, it has previously been hypothesized that a history of cancer could lead to increased surveillance and a lower threshold for interventions (Thomson et al. 2005 and Clark et al. 2007), which could also explain the increased risk for induction of labor and CS among cancer survivors.

One recent study by Sitras et al. showed that pregnant women with fear of childbirth and mental health problems had increased odds for choosing epidural analgesia compared to women without these conditions (Sitras et al. 2017). Cancer survivors are at risk for pain syndromes and also have an increased risk for fear of childbirth and mental disorder and diseases of the nervous system, so our hypothesis was that they might also have an increased use of medical pain relief during delivery compared to siblings. Pain is a common problem in cancer survivors, and according to a recent study (Karlson et al. 2018), 29% of adult childhood cancer survivors (median age 31 years) reported moderate to severe pain. Survivors with chronic health conditions, depression and anxiety were most likely to report chronic pain

(Karlson et al. 2018). The pain mechanism varies with cancer treatment. Surgery is known to potentially cause persistent postsurgical syndromes such as postmastectomy pain and phanthom limb pain (Glare et al. 2014), whereas radiotherapy can cause plexopathies and osteoradionecrosis (Dropho et al. 2010). The most common pain syndrome is generally thought to be chemotherapy-induced peripheral neuropathy, which is associated with specific chemotherapeutic agents (Glare et al. 2014). Our study found that 53.8% of the cancer survivors and 48.3% of their siblings received epidural analgesia during vaginal delivery. For any medical pain relief, epidural analgesia and spinal anaesthesia, the crude OR was increased but after adjusting for maternal age, year of delivery, gestational age and maternal smoking, only the risk for spinal anaesthesia was increased. It is notable, that data on spinal anaesthesia is only available from 2004 onwards, whereas data on epidural analgesia is available from 1987 onwards. A larger proportion of cancer survivors delivered after 2004 compared to siblings (43.4% and 28.7%, respectively), which might have affected the results. To our knowledge, use of medical pain relief in cancer survivors have not been studied before.

6.4 THE ASSOCIATIONS OF CANCER CHARACTERISTICS AND VARIOUS REPRODUCTIVE VARIABLES

6.4.1 AGE AT CANCER DIAGNOSIS

Cancer patients treated in their childhood had the lowest use of fertility treatments, whereas the overall use of fertility treatments and more extensive fertility treatments (ART) was highest among cancer survivors diagnosed as young adults (Study II). These results suggest that prepubertal cancer treatments might be less harmful to the ovaries than cancer treatments received postpubertally. Age at cancer treatment has been found to be an important determinant for POI in previous studies of cancer survivors (Petrek et al 2006, Letourmeau et al. 2012). The higher the age of the girl/woman when receiving cancer treatment, the smaller the follicle pool in the ovaries; therefore, a smaller dose of radiation or chemotherapy is needed to cause POI in women at a higher age compared to younger women (Wallace et al. 2005, Anderson et al. 2015).

As for maternal pregnancy-related conditions according to age at cancer diagnosis, the strongest association was observed in adolescents, for whom we observed an increased OR for overall hospitalization, hospitalization for vaginal bleeding and fear of childbirth compared to comparison subjects. However, the highest incidence of preterm delivery was observed in childhood cancer survivors

(Study III). We found no other studies measuring the same pregnancy-related outcomes as we did according to age at cancer diagnosis. Concerning the risk for preterm delivery according to age at cancer diagnosis, we found two other studies (Haggar et al. 2014 and Anderson et al. 2017) measuring the risk. Haggar et al.´ study (2014) found that the risk for preterm delivery increased with a higher age at cancer diagnosis. Anderson et al.´s study (2017) found that the risk was quite similar in all age groups. These studies, however, only included women diagnosed with cancer at the age of 15-39 years of age, leaving out childhood cancer survivors, for whom the incidence for preterm delivery was highest in our study.

Concerning adverse obstetric outcomes, childhood cancer survivors had the strongest association for these outcomes, as the OR for both induction of labor and CS was most increased in this diagnostic age group compared to siblings. Childhood cancer survivors were also the only diagnostic age group in which the OR for urgent CS was increased (Study IV). We found one study (van der Kooi et al. 2018) that compared delivery outcomes in the same diagnostic age groups as we did. In that study, childhood cancer survivors had the highest risk for elective CS (RR 3.15) and the lowest possibility for spontaneous vaginal delivery (RR 0.63). Similar to our study, the possibility for vaginal delivery increased with higher diagnostic age in cancer survivors. The higher risks for induction of labor and CS particularly in childhood cancer survivors are difficult to explain. It is possible that prepubertal cancer treaments on an undeveloped uterus are more harmful compared to postpubertal cancer treatments. Another explanation could be that CNS tumors, one of the most common childhood cancers, were associated with an increased risk for induction of labor and CS.

6.4.2 TIME BETWEEN CANCER DIAGNOSIS AND DELIVERY

Elapsed time between cancer diagnosis and delivery played a central role in the use of fertility treatments in cancer survivors giving birth. The use of fertility treatments increased over time, suggesting that cancer treatments lead to diminished ovarian reserve and a narrowed fertile time window in cancer survivors (Study II). This finding has been verified in a recent study (Levine et al 2018), where cancer survivors had a more than 10-fold increased risk for non-surgical premature menopause compared to siblings. Survivors with premature menopause had decreased pregnancy rates (RR 0.49) compared to survivors without premature menopause. Another study that supports our findings explored the use of ART in cancer survivors compared to healthy women (Luke et al. 2016) and found that the

live birth rate was reduced when autologous oocytes were used but that it was similar to healthy women when donor oocytes were used.

Regarding pregnancy-related conditions and adverse obstetric outcomes in cancer survivors, we could not identify any trends according to the time between cancer diagnosis and delivery except for overall hospitalization, for which the association was highest among cancer survivors receiving a cancer diagnosis 0-5 years before delivery (Study III and IV). No other studies measuring these pregnancy-related conditions according to elapsed time between cancer diagnosis and delivery, were found. Anderson et al.´s study (2017) measured the risk for adverse obstetric outcomes (preterm delivery and CS, among other outcomes) and identified no trends according to time between cancer diagnosis and delivery.

6.4.3 CANCER TYPE

Being a survivor of thyroid cancer was associated with an increased use of overall fertility treatments (Study II). This was an unexpected finding, as previous studies found that radioactive iodine treatment of thyroid cancer did not decrease pregnancy rates compared to controls (Stensheim et al. 2011) and only seemed to cause temporary amenorrhea (Sawka et al. 2008). However, according to a recent study (Yaisha et al. 2018) premenopausal women with differentiated thyroid cancer treated with radioactive iodine treatment had an increased risk for POI. The POI diagnosis was based on measurements of AMH levels in serum, which were 32% lower than prior to treatment even one year after radioactive iodine use. The oocytes in the ovaries are believed to be at risk for injury while exposed to ionizing radiation excreted through the urine (Yaisha et al. 2018).

Studying obstetrics outcomes according to cancer type, we found that being a survivor of CNS tumor was associated with an increased risk for CS (Study IV). This is in contrast to two other studies (Haggar et al. 2014, Reulen et al. 2017) in which they found an increased risk for CS in cancer survivors who suffered from leukemia, bone sarcoma or Wilms tumor but not CNS tumors. It is notable, however, that our analyses on pregnancy-related conditions and obstetric outcomes according to different cancer types resulted in such small numbers that they might affect the results.

6.4.4 CANCER TREATMENT

Our analyses that were stratified by cancer treatment, found no increased use of fertility treatments in the different treatment groups, with the exception of radioactive iodine treatment in thyroid cancer survivors, which was associated with an increased use of fertility treatments (Study II). Previous studies, however, found that radiation fields that include the ovaries and chemotherapy with alkylating agents cause the most extensive damage to the ovaries (Morgan et al. 2012, Anderson et al. 2015). Turcotte et al.´s study (2017) found that the use of alkylating agents has increased during recent years; it is possible that this could partly explain the increased use of fertility drugs in survivors. We found no association in our data between chemotherapy and an increased use of fertility treatments. It is impossible, however, to study outcomes by different chemotherapeutic agents or radiation doses from the FCR as this information is not available. We could roughly identify those who received abdominal radiotherapy by combining information on radiation and cancer site.

Radiotherapy is believed to damage the ovaries by a direct loss of follicles and oocytes in a dose-dependent manner (Anderson et al. 2015). The mechanism by which chemotherapy damages the ovaries is less clear, but alkylating agents are also believed to directly damage the follicles and the oocytes (Morgan et al. 2013).

Regarding pregnancy-related conditions, survivors in all treatments groups had an increased risk for overall hospitalization compared to comparison subjects. However, the risk was highest among survivors treated with surgery. Cancer survivors treated with chemotherapy had the highest amount of preterm deliveries (Study III). Similar results were found in Anderson et al.´s study (2017), whereas cancer survivors treated with radiotherapy had the highest risk for preterm delivery in Haggar et al.´s study (2014).

Concerning obstetric outcomes according to different cancer treatments, those treated with chemotherapy had the highest OR for induction of labor and overall CS. This group also had an increased OR for urgent CS. Similar results were observed in three other studies (Haggar et al. 2014, Anderson et al. 2017, Reulen et al. 2017) in which the risk for CS was highest among survivors treated with chemotherapy or without radiotherapy.

6.5 SUMMARY AND CLINICAL IMPLICATIONS

Our two studies on fertility treatments support previous findings (Barton et al. 2013) that cancer survivors have an increased risk for subfertility. During the most recent time period, from 2003 onwards the use of fertility treatments increased and were higher in cancer survivors compared to siblings. Elapsed time from cancer treatment and age at cancer diagnosis played a central role, and we found increased use of fertility treatments among women diagnosed with cancer as young adults and women receiving their cancer treatment a long time ago. A subclassification of fertility treatments into ART and OI revealed that the use of ART was higher in cancer survivors compared to siblings, whereas the use of OI was similar in both groups.

Studying fertility treatments in cancer survivors is of clinical importance, since the need for fertility treatments largely reflects the damage to the ovaries caused by cancer treatments. Use of fertility treatments in cancer survivors also mirrors the attitude and knowledge of the treating physicians and the cancer survivors themselves. Our results indicate a more active approach among clinicians towards fertility treatments in cancer survivors during the most recent years.

Thus, collaboration between oncologists and gynecologists is important in order to identify those at risk for infertility already when planning the cancer therapy, as well as for detecting ovarian dysfunction and POI later on. According to recent clinical guidelines (Oktay et al. 2018), the treating physician should discuss the possibility of infertility with all cancer patients or their parents/guardians as early as possible. Cancer survivors at risk of infertility should be provided options for fertility preservation. Oocyte and embryo preservations are standard methods that should be offered (Oktay et al. 2018). The field of ovarian tissue cryopreservation is advancing rapidly and will probably become a standard procedure in the future (Oktay et al. 2018). Alarmingly, according to a Swedish study (Armuand et al. 2012), only 48% of adult female cancer survivors reported that they received information of a possible reducement of their fertility due to cancer treatment. In contrast, males in the same study received information about the potential negative impact on fertility in 80% of the cases (Armuand et al. 2012). Another study found that infertility often came as a surprise for cancer survivors and that they had a false belief about their fertility (Oosterhuis et al. 2008).

Fertility preservation for prepubertal girls with cancer in Finland is considered if the risk for infertility is very high, whereas for postpubertal girls and adult women it is considered if the risk for infertility is high (Finnish National recommendations for fertility preservation 2019, Table 2). After the cancer treatments, childhood and

adolescent cancer survivors attend follow ups at the pediatric clinic until the age of 18 years. After that, the follow up for survivors with a high risk for late effects continues at late-effect clinics, established at all Finnish university hospitals. In some areas, survivors who are estimated to have a low risk for late effects can contact the late-effect clinic if needed, whereas the primary health care provider is responsible for the follow up in other areas. National Finnish guidelines recommend that all female childhood cancer survivors should be referred to a gynecologist after puberty onset (which is hormonally induced if spontaneous onset of puberty does not occur) to evaluate fertility and possible need for contraception. Ovarian reserve is evaluated by vaginal ultra-sound, estimating the AFC and by measuring the serum levels of AMH. Individual follow up based on the results is recommended.

Study III showed that the increased risk for preterm delivery in cancer survivors was at least partially due to maternal pregnancy-related conditions (vaginal bleeding and pre-eclampsia) which might be more severe in cancer survivors compared to controls, possibly leading to medically induced preterm delivery. However, we could not rule out the possibility that the history of cancer influenced the health-care provider or the pregnant woman, eventually leading to increased surveillance and a lower threshold for medical intervention (Thomson et al. 2005, Clark et al. 2007). This goes hand in hand with cancer survivors having an increased risk for hospitalization during pregnancy. Early onset cancer survivors have been found to have an increased risk (RR 1.87) for overall hospitalization in adult life compared to matched controls, probably due to late morbidities after cancer treatment (de Fine Licht et al. 2017). Regarding obstetric outcomes (Study IV), cancer survivors had small but significantly increased odds for induction of labor and elective CS. All in all, the possibility for a spontaneous vaginal delivery was reduced compared to siblings. Being a childhood cancer survivor, as well as being treated with chemotherapy was associated with the highest risks for adverse obstetric outcomes.

Health-care providers need to be aware of the increased risk for these pregnancy-related conditions and adverse obstetric outcomes and consider individualized follow up. Our results were generally reassuring, however, and most cancer survivors will experience a pregnancy and delivery without complications.

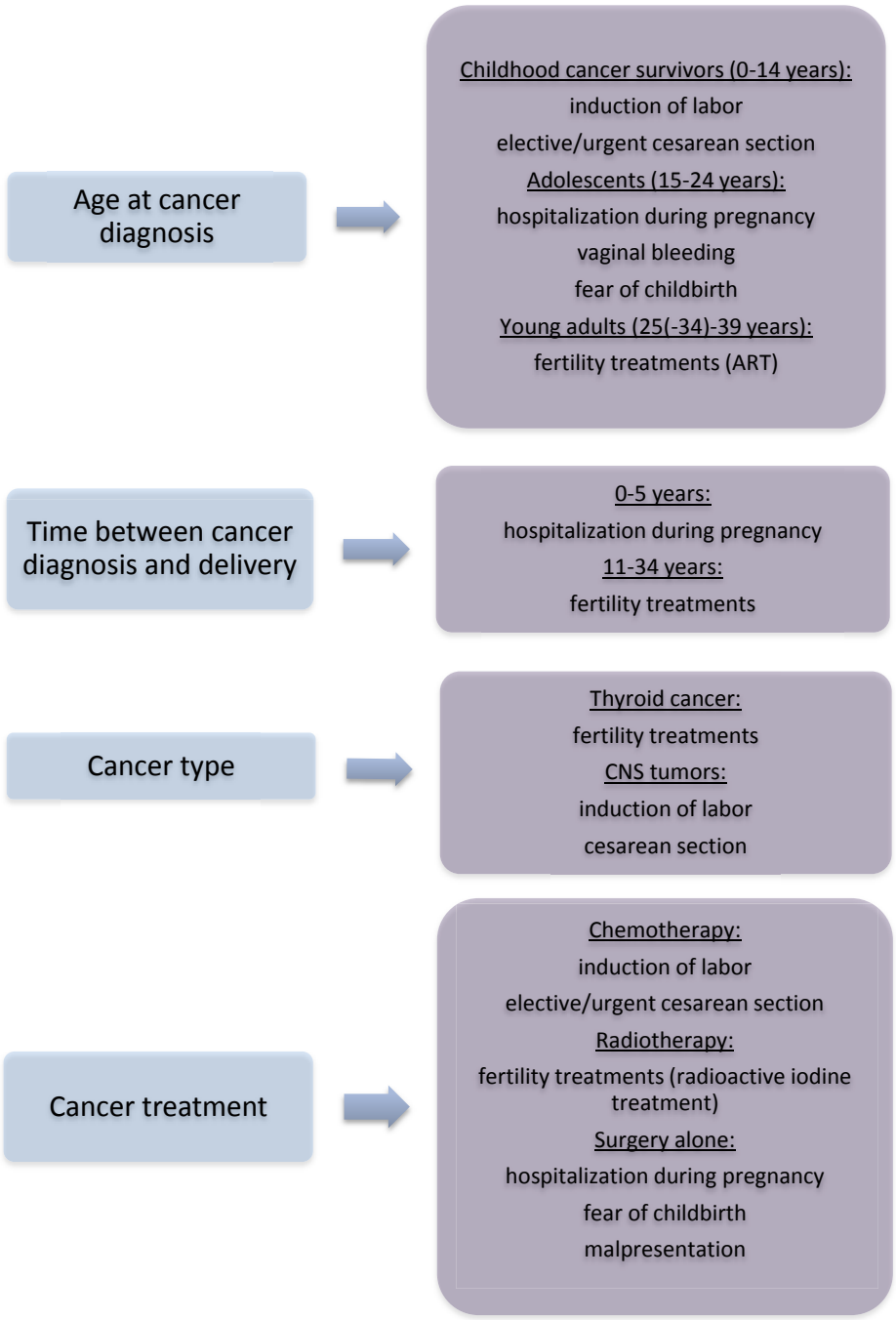

Figure 9 An overview of the associations of cancer characteristics and increased odds for different outcomes in our studies

6.6 STRENGTHS AND LIMITATIONS

The studies in this thesis were based on data from high quality Finnish health registers. Our registers enabled long-term follow up covering a large number of women. The coverage and completeness of these registers are exceptionally high (Teperi et al. 1993, Gissler et al. 2002, Leinonen et al. 2017), making it possible to follow practically all individuals, without recall or reporting bias. Previous studies on late effects in cancer survivors are often based on self-reported questionnaires and medical records (Robison et al. 2009, Leisenring et al. 2009). A limitation in those kind of studies is recall bias.

A challenge when studying late effects of early onset cancer survivors is that the cancer treatment protocols change rapidly, and new treatments are frequently introduced (Stark et al 2015). Many studies of late effects in cancer survivors date back to an era of treatments that are no longer in use (Hawkins et al. 2008). Regarding the reproductive outcomes studied in this thesis, the follow ups ended in December 2012 (Study I) and December 2013 (Study II, III and IV). Most studies on reproductive outcomes in cancer survivors reviewed in this thesis, with the exception of three (Anderson et al. 2017, Anderson et al. 2018, van der Kooi 2018), have follow ups ending before ours.

The FCR has a high coverage, 96% for solid tumors and 86% for hematologic malignancies (Leinonen et al. 2017). A limitation, however, is the incomplete data on cancer treatments, making it impossible to study outcomes by different chemotherapeutic agents or radiation doses. We could roughly identify cancer survivors who had received abdominal radiation by combining information on radiotherapy and the cancer site

The MBR made it possible for us to study a large number of different outcomes and provided information on important confounders, making it possible to adjust for factors that might affect the outcomes studied. We would have liked to adjust for the women´s socioeconomic status but that information was missing for more than 30% of the women. Information was probably lacking, because young women were studying or were at home with children. Instead, we adjusted for smoking, which is considered a good proxy for socioeconomic status (Jaakkola et al. 2001). As maternal obesity is increasing in women in the western world (Hansson et al. 2016) and has been found to affect many obstetric outcomes, it would have been important to adjust our analyses for obesity as well. However, as information on BMI was only available from 2004 onwards and missing in 6.6% of the cases, we decided not to include it in our analyses.

Study I used information on prescribed fertility drug purchases from the RPM as a proxy for fertility treatments in cancer survivors. Only a few previous studies have investigated the use of fertility treatments in cancer survivors in a population-based registry setting. Study I is to our knowledge the first to use a nationwide drug prescription register to explore use of fertility drugs in cancer survivors. Drugs or drug combinations, classified as fertility drugs in this study, are rarely used for other indications. Cancer survivors with a registration of aromatase inhibitor use as a cancer treatment in the RPM (frequently used in breast cancer patients), were excluded from the follow-up. By using siblings as a comparison cohort, we could adjust for familial factors that could affect the use of fertility treatments. The main limitation in this study was that information was missing on whether the fertility drug was used for fertility preservation or as fertility treatment. Furthermore, RPM does not provide information on whether autologous or donor oocytes were used in ART. In addition, women diagnosed with cancer in the most recent time period had a short follow up, which might affect the result. Pregnancy and live birth rates after fertility treatments were not included in this study.

Study II identified fertility treatments among cancer survivors and siblings giving birth. The main limitation in this study was that unsuccessful fertility treatments were not included. In the light of recent findings on clinical infertility and POI in cancer survivors (Barton et al. 2013, Anderson et al. 2015, Levine et al. 2018), we suspect that there were many cancer survivors with unsuccessful fertility treatments. A previous study showed that all fertility treatments are not documented in the MBR (Gissler et al. 2004). The information on fertility treatments is mostly received by self-report of the mother, and many women might consider this sensitive information that they do not want to reveal. We suspect that there is an underestimation of fertility treatments in the MBR. As this possible underestimation applies to both cancer survivors and their siblings, we consider our results valid.

The main strengths of Studies III and IV, were that we were able to produce novel information on several pregnancy-related conditions and obstetric outcomes that were never or rarely studied in cancer survivors before (IHC, fear of childbirth, mental disorders, placental pathologies, induction of labor, different subtypes of CS, to name a few). However, some of the outcomes studied were so rare (especially for sub-analyses stratifying by cancer type) that we could not draw conclusions concerning the odds in cancer survivors compared to comparison subjects/siblings. ICD-10 diagnoses are registered in the MBR from 2004 onwards. The registration of these ICD-10 diagnoses rely on the treating physician reporting them in the patients´ medical records. A patient with a less severe condition not requiring follow up at the

maternity clinic might not have an ICD-10 diagnosis in the MBR. For example, 10.8% of all cancer survivors in Study III were registered as having a pathological 2-h oral glucose tolerance test, the definition of GDM. However, only 8.7% of the cancer survivors ended up with an ICD-10 diagnostic code for GDM (O24.4 or O24.9) in the MBR. As this limitation concerned both cancer survivors and comparison subjects and siblings, we consider our results valid. However, pregnancy-related conditions and obstetric outcomes were analyzed whenever possible based on dichotomous variables in the MBR rather than on ICD-10 diagnoses.

Lastly, when identifying the reasons for preterm deliveries in cancer survivors in Study III, our results led us to suspect maternal pregnancy-related conditions necessitating medically induced preterm deliveries. However, we could not rule out surveillance bias in Studies III and IV, as the obstetricians might be influenced by the history of cancer, which might affect their decisions.

6.7 FUTURE ASPECTS

The survival rates are increasing for many cancer types, so it is of great importance that possible late effects are taken into account when choosing the cancer therapy. Continued research is needed to identify possible changes in occurrence of late effects, as new cancer treatments and treatment combinations are constantly being introduced. Cancer survivors are especially concerned about late effects on the reproductive system.

We showed that cancer survivors use more fertility treatments than their siblings. However, further studies are needed on pregnancy and live birth rates after the fertility treatments in cancer survivors. This is important, as reduced pregnancy and live birth rates after fertility treatments in cancer survivors would indicate that fertility preservation techniques are needed to a larger extent. To acquire more information on the indications for the fertility treatments in cancer survivors and their siblings, fertility treatment procedure codes could be linked to cancer survivors and siblings in addition to their use of fertility drugs.

Being a cancer survivor was associated with an increased risk for several pregnancy-related outcomes, not previously studied. More studies are needed to confirm these results. Pregnancy-related cardiotoxicity is a rare condition but important to study. In the future, a study linking the hospital discharge register to the MBR could be useful when studying this condition. However, pregnancies and deliveries in cancer survivors were typically uncomplicated and thus cancer survivors should not be discouraged to have children after their cancer is cured.

7 CONCLUSIONS

This thesis evaluated the reproductive health in female early onset cancer survivors. The following conclusions can be made:

1. Female cancer survivors have an increased use of fertility drugs compared to siblings, which can be explained by the increased use of assisted reproductive technology. Time period of drug purchase played a central role, and an increased use of assisted reproductive technology from 2003 onwards was observed (Study I).

2. Survivors, diagnosed in their childhood, have the lowest use of fertility treatments and seem to become pregnant with less extensive fertility treatments than survivors diagnosed as young adults. In cancer survivors giving birth, time elapsed from cancer treatment increases the use of fertility treatments over time, suggesting that cancer treatments lead to a diminished ovarian reserve and a narrowed fertile window (Study II).

3. Cancer survivors have an increased risk for preterm delivery, partially explained by certain maternal pregnancy-related conditions (vaginal bleeding and pre-eclampsia) that might be more severe in cancer survivors than in siblings. Being a cancer survivor is also associated with an increased risk for hospitalization during pregnancy and certain maternal pregnancy-related conditions (intrahepatic cholestasis, fear of childbirth, use of low molecular weight heparin, mental disorders and diseases of the nervous system), possibly leading to medically induced preterm delivery. The risk for spontaneous preterm delivery (preterm rupture of the amniotic membranes and threatened preterm labor) is not increased (Study III).

4. Being a cancer survivor is associated with an increased risk for induction of labor and elective cesarean sections. The highest risks for adverse obstetric outcomes were observed among childhood cancer survivors (Study IV).

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